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Diagnostic value of nerve growth factor in detrusor overactivity: a study on women with mixed urinary incontinence

Hanieh Salehi-Pourmehr[1] · Morteza Ghojazadeh[1] · Elham Jahantabi[2] · Sakineh Hajebrahimi[1,2]

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Abstract

Objective Urinary incontinence has a profound impact on women's quality of life. Studies have shown that changes in urinary protein levels could be a potential diagnostic biomarker in some urological diseases. The aim of present study is to determine the diagnostic value of nerve growth factor (NGF) in women with mixed urinary incontinence (MUI) as a diagnostic biomarkers of detrusor overactivity (DO).

Methods Seventy women aged between 20 and 75 years with MUI were enrolled in this prospective study. All participants underwent urodynamic study. Urine NGF levels were measured using an ELISA method. NGF level was compared between groups using Mann–Whitney *U* test. Receiver Operator Characteristic (ROC) analysis was employed to evaluate the diagnostic performance of urinary NGF.

Results The results showed that the median (min, max) of NGF in patients with DO was significantly higher in comparing to its level in women without DO [184.10 (31, 346.60) pg/ml vs. 151.80 (21, 210.70)], respectively ($P=0.035$). Using receiver-operator characteristics analysis, the threshold urinary NGF value of 102.00 pg/ml provided a sensitivity of 88% and specificity of 40% in diagnosing DO, PPV of 39.1%, and NPV of 88.2%, positive likelihood ratio 2.18 and negative likelihood ratio of 0.45 ($P=0.02$).

Conclusion Based on high sensitivity and low specificity, we can conclude that NGF can be a good tool for ruling out the OAB when the test is negative. However, the future investigations are needed to expand the observed correlation in larger groups of women with DO.

Keywords Biomarker · Overactive detrusor · Nerve growth factor · Sensitivity · Specificity

Introduction

Urinary incontinence (UI) is a common condition which is defined as the complaint of any involuntary leakage of urine [1]. Its prevalence in developing world's female is 25.7% (95% CI: 22.3–29.5). Besides, the prevalence rates for stress (SUI), urgency (UUI), and mixed (MUI: SUI and UUI) were 12.6% (95% CI: 10.3–15.4), 5.3% (95% CI: 3.4–8.3), and 9.1% (95% CI: 7.0–11.8), respectively, in a meta-analysis [2]. UI has a profound impact on the quality of life. The cost of treatment for these patients has been reported about 7 billion dollars in some countries of Europe, the United States, Canada, and the United Kingdom [3]. Overactive bladder (OAB) especially detrusor overactivity (DO) are among the common cause of UI. OAB is a clinical syndrome which is defined by the urgency with or without urgency UI, usually associated with daytime frequency and nocturia in the absence of proven infection or other specific causes [1]. Urgency is the key symptom of the OAB, which indicates a defect in the bladder sensory pathway that should, but not necessarily, be associated with DO in the cystometry [4]. Fifty-eight percent of women with wet OAB have DO in the urodynamic study [5]. Due to high burden of UI on patients, their family and health system, the diagnosis of its pathophysiology is highly recommended and treatment is depending on whether SUI or UUI is prioritized. The pathophysiology of SUI is urethral hypermobility or intrinsic sphincter

✉ Sakineh Hajebrahimi
hajebrahimis@gmail.com; ebrahimis@tbzmed.ac.ir

[1] Research Center for Evidence-Based Medicine, Iranian EBM Centre: A Joanna Briggs Institute (JBI) Center of Excellence, Tabriz University of Medical Sciences, Tabriz, Iran

[2] Urology Department, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

dysfunction, and the cause of ureteral hypermobility is the weakness of normal extrinsic support of the urethra, which is itself due to the weakness of the endopelvic fascia and pelvic floor muscles [6]. UUI can have many causes but is often due to DO. Based on underlying pathophysiology, the treatment methods vary. In SUI, anti-incontinence surgery is the main treatment, however, in the OAB, anti-incontinence surgery is not accompanied with good results, and the symptoms may alleviate only in half of the patients [7].

The real pathophysiology of MUI is not well understood, and anti-incontinence surgery in women with MUI can lead to more therapeutic failure and the persistence of UUI after surgery.

It may not be clinically easy to separate SUI and UUI. The clinical diagnosis of OAB is still based on subjective symptoms, and treatment based on possible clinical signs to eradicate the underlying pathophysiology of the UI.

However, the majority of women who complain of MUI still need an urodynamic study to diagnose DO before deciding to have anti-continence surgery. It is estimated that half of the women with OAB symptoms, do not have DO. Since, urodynamic is an invasive and expensive diagnostic method which is accompanied with different possible complications including urinary tract infections, bladder and urethral rupture, intolerance and acceptance of the patient, an objective and accurate as well as non-invasive method is needed to diagnosis and assessment the outcomes of therapeutic methods in OAB patients. Evidence has shown that changes in urinary proteins levels could be a potential biomarker for diagnosis of OAB, and bladder outlet obstruction [8]. Biomarkers such as nerve growth factor (NGF) has been shown that be an alternative simple and more cost-effective method for diagnosis of DO.

Regarding the limited studies to investigate the relationship between urinary NGF level in patients with DO and MUI, the aim of the present study is to examine the diagnostic value of urinary NGF in the detection of DO in women with MUI.

Materials and methods

Study population

This cross-sectional study was conducted from January 2016 to April 2017. After obtaining the approval of the Ethics Committee of Research and the vice-chancellor of the Tabriz University of Medical Sciences (66,054), women were recruited from tertiary urology referral center of teaching Imam Reza hospital, Tabriz, Iran.

The target population were 70 patients with MUI symptoms. Eligibility criteria included the willingness to participate in this study, aged between 20 and 75 years, no history of neurological dysfunction, bladder cancer, bladder or renal calculi, continence surgery, using of antimuscarinics at the time of recruitment, voiding dysfunction or urinary tract infection, neurogenic lesions or post-void residual volumes of more than 50 ml, bladder outlet obstruction or interstitial cystitis and prolapse (Grade 3 and 4 prolapse based on categorization (POP-Q).

Informed consent was obtained from all subjects before collecting urine. Urine samples were collected for measurement of NGF.

The International Consultation Incontinence Questionnaire—UI Short Form (ICIQ-UI SF) and International Consultation on Incontinence Questionnaire Overactive Bladder (ICIQ-OAB) were used for data collection. Brief and specific ICIQ-UI SF is a questionnaire consists of three items: (1) frequency of UI (never, once a week, two or three times a week, once a day, a few times a day, always); (2) volume (none, small amount, moderate amount, large amount); and (3) how much urine leakage affects your daily life (0: not at all; 1–3: mildly; 4–6: moderately; 7–9: severely; 10: to a great extent). From the sum of these three items, the total ICIQ-UI SF score (between 0 and 21) was calculated. A fourth item included eight questions related to the symptoms to determine the type of UI. The validity of the Persian version of ICIQ_SF has been approved previously [9, 10].

The ICIQ-OAB provides the impact of OAB symptoms on the patient's quality of life and outcome of treatment. This questionnaire is used to screen OAB in both primary and secondary care institutions. Four question items include frequency, nocturia, urgency and urge urinary incontinence. The range of scores varies between 0 and 16, with greater values indicating increased symptom severity. The validation of ICIQ-OAB questionnaire Persian version also was determined previously by Sari-Motlagh et al. [11].

Urodynamic assessment

All patients after accurate pelvic examinations underwent urodynamic study. Based on the urodynamic outcome according to the urodynamic protocol, patients were divided into two categories: those who had DO with MUI, and those who did not have.

NGF assays

Urine sample was collected just before urodynamic in all eligible women. Immediately after gathering the urine samples, they were put on ice and transferred to the laboratory. The urine samples were centrifuged at 3000 g for 10 min at 4 °C. The supernatant was separated into aliquots in 1.5-mL tubes and preserved in a freezer at − 80 °C for further analysis. Urinary NGF levels were measured by enzyme-linked

immunosorbent assay (ELISA) (Promega, Madison, WI, USA), with a precise and highly sensitive ELISA kit, which had a minimum sensitivity of 7.8 pg/ml. Assays were performed according to the manufacturer's instructions. All samples were run in triplicate, and the values were averaged.

Statistical analyses

Data were analyzed using SPSS software (SPSS 21, SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to examine the frequency distribution, mean and Standard Deviation (SD). To answer the questions of the research, Independent sample's *T* test and non-parametric Mann–Whitney *U* test were used for continuous variables. The total urinary NGF levels were compared among MUI patients with or without DO using Mann–Whitney *U* test. The NGF levels were also compared between the two groups. Pearson's correlation coefficient was used for analyzing the correlation between the variations in urinary NGF levels, age, and ICIQ-OAB, and ICIQ-UI SF. The Kolmogorov–Smirnov test and *Q*–*Q* plot were used to examine the normal distribution of continuous variables. Receiver-operator characteristics curves (ROC) were used for calculation of areas below curves and to analyze the sensitivity and specificity of threshold values of urinary NGF for differentiation of DO in women with MUI. $P < 0.05$ was considered as statistically significant.

Results

A total of 70 women with MUI were recruited. Of these, 39 women, according to the results of urodynamic had DO. The range of participant's age was between 25 and 73 years. There was no significant difference in the mean age between the two groups [49.74 ± 10.65 vs. 48.71 ± 9.04, $P = 0.67$ for DO patients or without it, respectively].

The minimum age of patients in MUI-DO group was 25, and the maximum was 72 years old. In women without DO, these amounts were 34, and 73 years, respectively. Half of women in both groups were older than 50 years old (48.4% in non-DO patients vs. 46.2% in DO groups).

The results showed that the median (min, max) of NGF in patients with DO was significantly higher than of women without DO [184.10 (31, 346.60) pg/ml vs. 151.80 (21, 210.70)], respectively ($P = 0.035$) (Table 1).

Using Pearson's correlation, there was a moderate positive correlation between the DO and NGF concentration in the study (Pearson correlation = 0.45; $P = 0.02$); but this correlation was not seen with age ($P = 0.43$).

ROC curve was used to determine the diagnostic accuracy of measuring urinary NGF concentration in differentiating the MUI-DO and MUI without DO. Using receiver-operator characteristics analysis, the threshold urinary NGF value of 102.00 pg/ml provided a sensitivity of 88% and specificity of 40% in diagnosing DO (Fig. 1). The areas under the ROC curve, (AUC) values, SE, and 95% CI for measurement of urinary NGF are summarized in Table 2.

Likelihood ratio (LR) indicates the pre-test to post-test probability to detect the disease. LR+, likelihood ratio of positive diagnostic test between 1 and 2 are minimal, LR+

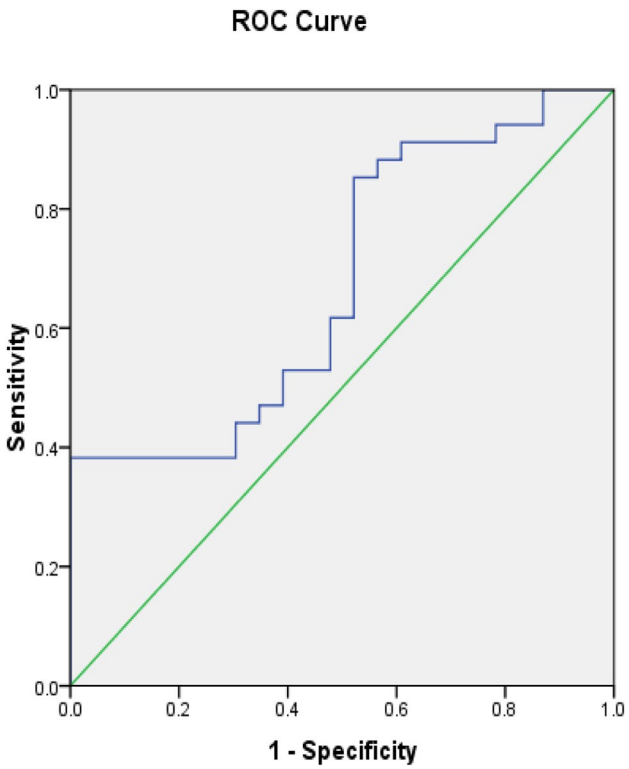

Fig. 1 Area under the ROC curve for measurement of NGF levels in DO patient

Table 1 The NGF concentrations among two groups

Groups	*N*	Median (min, max) NGF	*P* value
MUI-DO*	39	184.10 (31, 346.60)	0.035
MUI without DO	31	151.80 (21, 210.70)	

**MUI* Mixed Urinary incontinence; *DO* detrusor overactivity; *NGF* nerve growth factor

Table 2 The areas under the ROC curve, SE, and 95% CI for measurement of urinary NGF concentration in two groups

AUC*	Standard error	95% confidence interval	*P* value
0.67	0.07	0.53–0.81	0.02

**AUC* area under curve

> 2 and < 5 are moderate, LR+ > 5 and < 10 are good, and LR+ > 10 is excellent [12]. In our study, the LR+ was 2.18 that shows the moderate predictive value of NGF in diagnosis DO.

We assessed the correlation between NGF level, and the scores of ICIQ-OAB, and ICIQ-UI SF in two categorized group of MUI patients with DO, or without it. There was not any correlation between NGF level, and ICIQ-OAB, and ICIQ-UI SF scores in both groups ($P > 0.05$). However, there was a statistically significant correlation between the scores of both questionnaires ($P = 0.033$) (Table 3).

Discussion

Our results showed that the median of NGF in MUI patients with DO was significantly higher in comparing to its level in MUI women without DO. Using receiver-operator characteristics analysis, the threshold urinary NGF value of 102.00 pg/ml provided a sensitivity of 88% and specificity of 40% in diagnosing DO, PPV of 39.1%, and NPV of 88.2%, positive likelihood ratio 2.18 and a negative likelihood ratio of 0.45 ($P = 0.02$).

Liu et al. in their study on women with frequency urgency and/or urgency incontinence showed that serum NGF levels were significantly elevated in OAB (median and interquartile range, 7.367 pg/ml, 0–57.66) compared to the controls (0.0728 pg/ml, 0–0.234, $P < 0.001$). Using the ROC analysis, the area below curve was highest in NGF levels (0.897) between OAB-wet and the controls (patients without lower urinary tract symptoms). In their research, cutoff urinary NGF value of 1.265 pg/ml provided a sensitivity of 87.7% and specificity of 80%. The area below curve was 0.765 for urinary NGF level in differentiation between overall OAB patients and the controls, respectively [13].

This issue which the urinary proteins such as NGF and prostaglandin E2 levels increase in patients with OAB, bladder outlet obstruction, and DO [14, 15] has been raised in recent years. Neurotrophins are necessary growth factors for differentiation, survival, proliferation and activities maintenance of central and peripheral nervous system's neurons [16]. Urothelium and smooth muscle are responsible for NGF production in the urinary tract [17]. Increment in the urinary NGF level may occur in both physiologic (e.g., in urgency) and pathologic conditions, and hence, as a biomarker, it may be an alternative simple and more cost-effective method for DO diagnosis. This study's results showed that MUI patients with DO had higher urinary NGF levels rather than non-DO cases. In normal conditions, NGF level in the urine is low. In response to bladder enlargement, sympathetic and sensory hyper-innervation, OAB [18, 19], and mechanical stretching [20], its production from bladder smooth muscle, and urothelial cells, and urinary bladder sensory afferent neurons are increased [21].

Previous studies demonstrated a higher urinary NGF level in both OAB women with or without UI [14, 22]. NGF acts as a chemical mediator, and by altering the properties or expression of Na or K channels in bladder afferent fibers, provoke bladder overactivity [23]. Therefore, treatment methods based on changing the NGF levels or alter the properties of these channels may be a promising management method for bladder dysfunction. In addition to the urinary NGF, PGE2 and cytokines are also higher in OAB patients and successfully decreased after treatment by antimuscarinic or Botox injection [24]. As mentioned, inflammation can lead to NGF rising, and chronic bladder inflammation in a biopsy specimen of idiopathic DO [25] is demonstrated. Vijaya et al. [26] showed higher levels of NGF in patients with SUI in comparing to normal controls. In the present study, the results provide evidence that women with MUI and DO had higher urinary NGF levels rather than women without DO suggesting that DO is a chronic inflammatory disorder with highly expressed urinary NGF.

Applying ROC analysis, the ability of NGF concentration in the diagnosis of DO and the non-DO group was good, where AUC value was nearly 0.7.

At present study, the sensitivity of urinary NGF levels in detecting DO among known MUI subjects was significantly high. Kuo et al. found that the sensitivity and specificity of this test in the diagnosis of OAB was 67.9% and 93.8%, respectively [21]. Vijaya et al. [26] study by ROC analysis demonstrated poor discriminant ability between different symptomatic groups and urodynamic groups. Using a cutoff of 13.0 ng NGF/Cr, the test provides a sensitivity of 81%, but a specificity of only 39% for OAB. It is in accordance with the result of our study.

Antunes-Lopes reported low values of sensitivity and specificity for NGF/Cr ratio with an AUC in ROC analysis of only 0.68 for OAB [27]. However, Liu investigated sensitivity of 84.9% and specificity of 84.5% in a 0.085 threshold for urinary NGF/Cr concentration for differentiation of OAB-wet and controls [14].

Table 3 Sensitivity, specificity, PPV, NPV, LR+, LR− and *p* value for NGF in differentiating DO in MUI patients

NGF (pg/ml)	Sensitivity (%)	Specificity (%)	PPV	NPV	LR +	LR−	*p*
	88	40	39.1%	88.2%	2.18	0.45	0.02

PPV positive predictive value; *NPV* negative predictive value; *LR+* positive likelihood ratio; *LR−* negative likelihood ratio

The present study was further analyzed to calculate its likelihood ratio (LR). This ratio indicates the pre-test to post-test probability to detect the disease [28]. LR+, likelihood ratio of positive diagnostic test between 1 and 2 are minimal, LR+ > 2 and < 5 are moderate, LR+ > 5 and < 10 are good, and LR+ > 10 is excellent [12]. In our study, the LR+ was 2.18 that shows the moderate predictive value of NGF in diagnosis DO.

Evidence-based publications in urology [29] have reported the measurement of urinary NGF levels in different types of bladder dysfunction such as OAB, painful bladder syndrome, idiopathic or neurogenic DO, and bladder outlet obstruction. The majority of them investigated rising urinary NGF levels in these conditions in comparing to healthy controls, and in response to therapeutic methods, its level is reduced. Most of these publications stated that the measurement techniques require standardization as well as validating the different antibodies to NGF.

The current study has some limitations. This study is a cross-sectional one which random urine sample collection may be accompanied with altered urinary biomarker level. Besides, we could not evaluate the ratio of NGF/Cr, because, in some patients, its level was reported randomly, and in the others, 24-h concentration was reported. We found only few studies which reported the urinary NGF values in other pathologic bladder condition, rather than MUI [13]. Hence, we could not compare our urinary NGF cutoff point with previous research.

Despite low specificity of urinary NGF (due to the high amount of false-positive results), NGF is potential objective biomarkers for DO. If its urinary level is negative, we may rule out DO based on sensitivity and NPV results. However, we cannot say definitively that it is superior to any other biomarkers or that it can replace current urodynamic measurements, and its measurement may be advised only before invasive urodynamics study to rule out DO. In addition, a definition of urinary NGF normal range is still required before it can be used as a diagnostic and prognostic tool.

One of our limitation was the lack of healthy control arm. Therefore, it is recommended the future studies with normal control women compare the results of NGF levels with MUI patients. In addition, we did not perform urodynamic and urine sampling multiple times in patients to see the presence of intra-patient variability in the emergence of DO and NGF levels.

Conclusion

Based on high sensitivity and low specificity, we can conclude that NGF can be a good tool for ruling out the OAB when the test is negative. However, future investigations are needed to expand the observed correlation in larger groups of women with DO.

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Author contributions HS-P: conceptualization, data collection, and drafted the manuscript. MG: methodology and data analysis. EJ: urodynamic assessment. SH: conducting a research and investigation process, oversight and leadership responsibility for the research activity planning and execution. All the authors approved the final version of manuscript.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Haylen BT, Freeman RM, Swift SE, Cosson M, Davila GW, Deprest J et al (2011) An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) and grafts in female pelvic floor surgery. Neurourol Urodyn 30(1):2–12
2. Mostafaei H, Sadeghi-Bazargani H, Hajebrahimi S, Salehi-Pourmehr H, Ghojazadeh M, Onur R et al (2020) Prevalence of female urinary incontinence in the developing world: a systematic review and meta-analysis—a report from the developing world committee of the International Continence Society and Iranian Research Center for evidence based medicine. Neurourol Urodyn 39(4):1063–1086
3. Milsom I, Coyne KS, Nicholson S, Kvasz M, Chen C-I, Wein AJ (2014) Global prevalence and economic burden of urgency urinary incontinence: a systematic review. Eur Urol 65(1):79–95
4. Hashim H, Abrams P (2007) Overactive bladder: an update. Curr Opin Urol 17(4):231–236
5. Hashim H, Abrams P (2006) Is the bladder a reliable witness for predicting detrusor overactivity? J Urol 175(1):191–194
6. McGuire EJ (2004) Pathophysiology of stress urinary incontinence. Rev Urol 6(Suppl 5):S1–S7
7. Demaagd GA, Davenport TC (2012) Management of urinary incontinence. P T 37(6):345–361
8. Kuo HC (2012) Potential biomarkers utilized to define and manage overactive bladder syndrome. LUTS Lower Urinary Tract Symptoms 4:32–41
9. Hajebrahimi S, Nourizadeh D, Hamedani R, Pezeshki MZ (2012) Validity and reliability of the International consultation on incontinence questionnaire-urinary incontinence short form and its correlation with urodynamic findings. Urol J 9(4):685
10. Rafii F, Shareinia H, Seyedalshohahadaee M, Sarraf P, Mahmoodi F (2014) The effect of pelvic floor muscle exercise training on urinary incontinence in patients with multiple sclerosis. Iran J Nurs 27(87):43–54
11. Sari Motlagh R, Hajebrahimi S, Sadeghi-Bazargani H, Joodi Tutunsaz J (2015) Reliability and validation of the international consultation on incontinence questionnaire in over active bladder to Persian language. LUTS Lower Urinary Tract Symptoms 7(2):99–101

12. Arnolds M, Oelke M (2009) Positioning invasive versus noninvasive urodynamics in the assessment of bladder outlet obstruction. Curr Opin Urol 19(1):55–62
13. Liu HT, Kuo HC (2009) Urinary nerve growth factor levels are elevated in patients with overactive bladder and do not significantly increase with bladder distention. Neurourol Urodyn 28(1):78–81
14. Liu HT, Chen CY, Kuo HC (2011) Urinary nerve growth factor in women with overactive bladder syndrome. BJU Int 107(5):799–803
15. Tyagi P, Barclay D, Zamora R, Yoshimura N, Peters K, Vodovotz Y et al (2010) Urine cytokines suggest an inflammatory response in the overactive bladder: a pilot study. Int Urol Nephrol 42(3):629–635
16. Allen SJ, Dawbarn D (2006) Clinical relevance of the neurotrophins and their receptors. Clin Sci 110(2):175–191
17. Steers W, Kolbeck S, Creedon D, Tuttle J (1991) Nerve growth factor in the urinary bladder of the adult regulates neuronal form and function. J Clin Investig 88(5):1709–1715
18. Chan R, Munoz A, Wenker EP, Stewart J, Boone T, Khavari R (2015) The association of urinary nerve growth factor levels with bladder outlet obstruction in women. Female Pelvic Med Reconstr Surg 21(2):111
19. Liu H-T, Chen C-Y, Kuo H-C (2010) Urinary nerve growth factor levels in overactive bladder syndrome and lower urinary tract disorders. J Formos Med Assoc 109(12):862–878
20. Yamaguchi O (2004) Response of bladder smooth muscle cells to obstruction: signal transduction and the role of mechanosensors. Urology 63(3):11–16
21. Kuo H-C, Liu H-T, Chancellor MB (2010) Can urinary nerve growth factor be a biomarker for overactive bladder? Rev Urol 12(2–3):e69
22. Liu H-T, Kuo H-C (2008) Urinary nerve growth factor level could be a potential biomarker for diagnosis of overactive bladder. J Urol 179(6):2270–2274
23. Steers WD, Tuttle JB (2006) Mechanisms of disease: the role of nerve growth factor in the pathophysiology of bladder disorders. Nat Clin Pract Urol 3(2):101–110
24. Liu H-T, Chancellor MB, Kuo H-C (2009) Urinary nerve growth factor levels are elevated in patients with detrusor overactivity and decreased in responders to detrusor botulinum toxin-A injection. Eur Urol 56(4):700–707
25. Apostolidis A, Jacques TS, Freeman A, Kalsi V, Popat R, Gonzales G et al (2008) Histological changes in the urothelium and suburothelium of human overactive bladder following intradetrusor injections of botulinum neurotoxin type A for the treatment of neurogenic or idiopathic detrusor overactivity. Eur Urol 53(6):1245–1253
26. Vijaya G, Cartwright R, Bhide A, Derpapas A, Fernando R, Khullar V (2016) Reliability and validity of urinary nerve growth factor measurement in women with lower urinary tract symptoms. Neurourol Urodyn 35(8):944–948
27. Antunes-Lopes T, Carvalho-Barros S, Cruz CD, Cruz F, Martins-Silva C (2011) Biomarkers in overactive bladder: a new objective and noninvasive tool? Advances in urology 2011:382431
28. Irwig L, Bossuyt P, Glasziou P, Gatsonis C, Lijmer J (2002) Designing studies to ensure that estimates of test accuracy are transferable. BMJ (Clinical research ed) 324(7338):669–671
29. Hajebrahimi S, Dahm P, Buckingham J (2009) Evidence-based urology in practice: the Cochrane library. BJU Int 104(8):1048–1049