Correlation between the NGF levels and questionnaire forms in patients receiving antimuscarinic treatment and those receiving onabotulinum toxin-A injection

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ABSTRACT

Objective: To compare nerve growth factor (NGF) levels in patients who received antimuscarinic, versus onabotulinum toxin-A (onaBoNT-A) injection, as well as to investigate whether there is a correlation between NGF levels, and 8-item overactive bladder questionnaire(OAB-V8), urogenital distress inventory (UDI)-6, and incontinence impact questionnaire (IIQ)-7 forms.

Material and methods: Fourty adult patients with OAB were enrolled in this prospective study. An antimuscarinic was prescribed to 20 naive patients, and onaBoNT-A injection was administered to 20 patients, who were refractory to antimuscarinics. Urine samples were obtained before, and after 3rd and 6th months of treatment, and NGF levels were measured. Symptom scores of OAB-V8, UDI-6,and IIQ-7 were recorded.

Results: There was no significant difference between groups in terms of the initial OAB-V8, IIQ-7, and UDI-6 scores, whereas NGF values showed no significant difference over time in onaBoNT-A group (p=0.069, p=0.069). NGF levels were significantly lower in 3rd and 6th months, in patients receiving antimuscarinic (p=0.003, p=0.007); a strong correlation was found in 3rd month between the NGF levels, OAB-V8 scores (r=0.704, p=0.001), and IIQ-7 scores (r=0.676, p=0.001), and a moderate correlation between NGF levels, and UDI-6 scores (r=0.583, p=0.007). In the 6th months, a very strong correlation was found between NGF levels, and OAB-V8 scores (r=0.811, p=0.004), and a strong correlation was found between NGF levels, and IIQ-7 scores (r=0.671, p=0.001). In onaBoNT-A group, there was no significant correlation between NGF levels, and other variables.

Conclusion: NGF level might be a good marker to evaluate effectiveness of treatment in patients receiving antimuscarinics, owing to correlation of urinary NGF levels with symptom scores. Lack of correlation in patients receiving onaBoNT-A injection could be a result of differences in the mechanism of action.

Keywords: Antimuscarinic; nerve growth factor; onabotulinum toxin-A; questionnaire forms.

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Introduction

The nerve growth factor (NGF) was discovered in 1986 by Stanley Cohen and Rita Levi-Montalci, which led the researchers to winning the Nobel Prize in Physiology or Medicine in the same year. NGF has been demonstrated as an effective molecule for the survival and maturation of the neurons developing in the peripheral nervous system. The introduction of systems that can precisely and sensitively measure the NGF protein levels, NGF receptors, and the specific messenger RNAs have shown that NGF plays an important role in both peripheral and central nervous systems. NGF is a member of the neurotrophin family, which includes the brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4, and it shows a high degree of structural similarities with these molecules.[1]

Urinary NGF level has been previously shown to increase in many patients with overactive bladder (OAB). As a biomarker, NGF may help to address the ideal candidates for drug or minimally invasive therapies in patients with OAB. A biomarker should be a characteristic that is objectively measured and evaluated as

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an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. A suitable biomarker needs to be easily accessible, reliable, and repeatable as a test and offering high specificity and sensitivity to diagnose and monitor OAB at the same time. There should be a relationship with the severity of OAB.[2]

In this study, we aimed to compare the NGF levels in the urine samples before and after the treatment of OAB in patients who received antimuscarinic therapy and onabotulinum toxin-A (onaBoNT-A) injection as well as to investigate whether there is a correlation between the NGF levels and the 8-item overactive bladder questionnaire (OAB-V8), urinary distress inventory- short form (UDI-6), and incontinence impact questionnaire-short form (IIQ-7).

Material and methods

Study participants

Between August 2017 and May 2019, a total of 40 adult patients with OAB were enrolled in this prospective study after Gaziantep University Ethics Committee approval (decision no:2016/313). Within the scope of the study, an antimuscarinic agent (solifenacin, 5 mg) was prescribed to 20 naive patients (15 women, 5 men) (group 1) who did not respond to behavioral therapies and/or conservative treatment. In group 2, 20 patients (16 women, 4 men) with OAB who did not respond to behavioral therapies and/or conservative treatment, including the administration of 2 different antimuscarinic agents and/or mirabegron for the last 3 months, were selected for onaBoNT-A injection. A single onaBoNT-A injection was administered to all the patients in group 2. Informed consent forms were signed by the patients before the treatments.

Patients who had genuine-stress type urinary incontinence, neurogenic bladder, pelvic organ prolapse (pelvic organ prolapse quantification system ≥3), interstitial cystitis (bladder pain syndrome), pelvic radiotherapy, bladder outlet obstruction (voiding) symptoms, Qmax<10 mL/s in men and Qmax<15 mL/s in women measured by uroflowmetry, a post-void residual urine volume (PVR) >100 mL, pelvic and incontinence surgery, and onaBoNT-A allergy were excluded from the study. In addition, patients who did not accept or were not able to perform a clean intermittent catheterization were considered ineligible for the study.

Main Points:

- While NGF values did not show significant change over time in the patients who underwent onaBoNT-A injection, it was found to be significantly lower in the patients received antimuscarinic treatment.
- Urine NGF levels might be a good marker to evaluate the effectiveness of treatment of OAB in patients receiving antimuscarinic therapy, due to urinary NGF levels correlate with the symptom scores.
- This lack of correlation in onaBoNT-A injection could be a result of differences in the mechanism of action.

Questionnaire forms

The patients who were enrolled in the study were informed about filling the following OAB questionnaires in the 3rd and 6th month follow-ups: OAB-V8, UDI-6, and IIQ-7.[3,4] The OAB-V8 form includes 8 questions that ask about how much do the complaints disturb the patients, and they are rated as not at all (0), a little bit (1), somewhat (2), quite a bit (3), a great deal (4), and very great deal (5). The UDI-6 inquiry form includes 6 questions that ask about the frequency of urogenital complaints and are graded as not at all (0), a little bit (1), moderately (2), and greatly (3). The IIQ-7 includes 7 questions that inquire about the effects of urinary incontinence on the patients' quality of life and are graded as not at all (0), slightly (1), moderately (2), and greatly (3).

Nerve growth factor level measurement

We checked urinary tract infection for standardized NGF measurement at each visit. Urine sampling was performed after treatment in patients with urinary tract infections. The NGF levels in the urine of patients were determined using Biont® Human NGF enzyme-linked immunosorbent assay kit. To measure the urine NGF levels, 5 mL of urine was centrifuged for 10 minutes, and the supernatant fraction was separated from the precipitating part and stored at –80^{0}C in a nitrogen tank.

Urine samples were taken from the patients, and the NGF levels were measured before and after treatment in the 3rd and 6th month follow-ups. The correlation between the patients' NGF levels and the OAB-V8, UDI-6, and IIQ-7 symptom scores was examined.

Onabotulinum toxin-A injection technique

Urine analysis was performed before the intervention, and antibiotic prophylaxis was administered during the procedure. OnaBoNT-A (100 units) was diluted with 10 cc of serum physiological solution. Under general anesthesia, a cystoscope was introduced into the urinary bladder. The bladder was filled with 100 cc, and injections at 20 different points were performed within the detrusor (except trigone) with a 25-G flexible needle of 35 cm length. Most of our patients were discharged on the same day as soon as they were able to void.

Statistical analysis

The data for normal distribution were tested by the Shapiro-Wilk test. The Mann–Whitney U test was used to compare the non-normally distributed variables in 2 independent groups, and the

Friedman and Dunn's multiple comparison tests were used for evaluating them at 2 different times. The Spearman correlation coefficient was used to test the relationships between numeric variables. The Statistical Package for the Social Sciences for (IBM SPSS Corp.; Armonk, NY, USA) Windows version 22.0 was used for statistical analysis, and $p<0.05$ was considered statistically significant.

Results

No significant difference was found among the mean age of the patients included in the study (antimuscarinic group: 39.1±12.22 years, onaBoNT-A group: 48.26±17.94 years; p=0.073). All patients consulted at the 3rd month follow-up; however, only 50% (n=10) of the patients who received antimuscarinic therapy and 30% (n=6) of the patients who underwent onaBoNT-A injection referred at the 6th month follow-up.

There was no significant difference between the 2 groups in terms of the average pre-treatment OAB-V8, IIQ-7, and UDI-6 scores (Table 1). The NGF levels were found to be significantly higher in the antimuscarinic group before treatment and at the 3rd month follow-up. Although the NGF levels showed insignificant changes over time in the onaBoNT-A group (p=0.069), a significant decrease was observed in the antimuscarinic group at the 3rd and 6th month follow-ups (p=0.003, p=0.007, respectively) (Table 2).

The relationship between the NGF levels and other variables is shown in Table 3. A strong positive correlation was found for the antimuscarinic group in the 3rd month between the NGF levels and OAB-V8 scores (r=0.704, p=0.001) and IIQ-7 scores (r=0.676, p=0.001). In addition, there was a moderate positive correlation between the NGF levels and UDI-6 scores in the 3rd month for the antimuscarinic group (r=0.583, p=0.007). At the 6th month follow-up, a very strong positive correlation was found between the NGF levels and OAB-V8 scores (r=0.811, p=0.004) and a strong positive correlation was found between the NGF levels and IIQ-7 scores (r=0.671, p=0.001) for the antimuscarinic group. In the onaBoNT-A group, there was no significant correlation between the NGF levels and other variables.

Discussion

In recent years, studies have strived to present the etiopathogenesis of OAB, find objective diagnostic methods, and provide treatment monitorization. Most of them focused on the hypothesis whether biochemical markers, which were found in increased levels in the urine, could be used as diagnostic tools. Among the biochemical markers mentioned in the literature, NGF comes to the forefront, considering its higher specificity. NGF is produced by the human bladder, and the human bladder contains sensorial fibers with high affinity to tropomyosin receptor kinase A. Animal studies have also shown that NGF is secreted by the bladder smooth muscles and urothelium.[5] In a study by Kim et al.[6] with 65 patients with OAB and 20 control patients, the levels of urine NGF were sig-

Table 1. OAB-V8, IIQ-7, and UDI-6 values before treatment and at 3rd and 6th month follow-ups of the treatment

	(n)	Antimuscarinic group	(n)	onaBoNT-A group	p
OAB-V8 (before treatment)	20	26.4±7.78	20	28.74±4.89	0.375
OAB-V8 (3rd month)	20	19.3±8.54	20	19.58±8.24	0.944
OAB-V8 (6th month)	10	19.4±10.62	6	23.67±10.91	0.479
IIQ-7 (before treatment)	20	13.25±3.7	20	14.89±2.6	0.127
IIQ-7 (3rd month)	20	9.95±3.86	20	9.79±3.24	0.832
IIQ-7 (6th month)	10	10.3±5.42	6	11±3.35	0.586
UDI-6 (before treatment)	20	10.65±3.83	20	10.26±3.28	0.746
UDI-6 (3rd month)	20	8.3±4.19	20	7.21±3.14	0.396
UDI-6 (6th month)	10	8.8±4.24	6	9.83±2.71	0.478

OAB-V8: 8-item overactive bladder questionnaire; UDI-6: urinary distress inventory, short form; IIQ-7: incontinence impact questionnaire, short form; onaBoNT-A: onabotulinumtoxin-A; n: number of patients

Table 2. Nerve growth factor levels before treatment and at the 3rd and 6th month follow-ups

	Before treatment	3rd month	6th month	p
Antimuscarinic group	45.86±16.35	29.56±10.26	29.56±11.82	0.004*
onaBoNT-A group	28.78±12.64	16.54±10.51	16.88±12.13	0.069

*p<0.05 were accepted as statistically significant. onaBoNT-A: onabotulinumtoxin-A

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Table 3. Correlation between nerve growth factor levels and questionnaire forms

			n	OAB-V8	IIQ-7	UDI-6
Antimuscarinic group	Before treatment	NGF	20	r=0.191 p=0.421	r=0.184 p=0.438	r=0.222 p=0.346
	3rd month	NGF	20	r=0.704 p=0.001*	r=0.676 p=0.001*	r=0.583 p=0.007*
	6th month	NGF	10	r=0.811 p=0.004*	r=0.671 p=0.034*	r=0.474 p=0.166
Onabotulinumtoxin-A group	Before treatment	NGF	20	r=–0.196 p=0.422	r=–0.327 p=0.171	r=–0245 p=0.321
	3rd month	NGF	20	r=0.343 p=0.150	r=0.287 p=0.233	r=0.083 p=0.736
	6th month	NGF	6	r=0.486 p=0.329	r=0.286 p=0.230	r=0.494 p=0.320

*p<0.05 were accepted as statistically significant. OAB-V8: 8-item overactive bladder questionnaire; UDI-6: urinary distress inventory, short form; IIQ-7: incontinence impact questionnaire, short form; NGF: nerve growth factor; r: Spearman rank correlation; n: number of patients

nificantly higher in the OAB group (p=0.005). Antunes-Lopes et al.[7] observed that the urine NGF levels were found to be 12 times higher in OAB patients than in the normal population. In a meta-analysis by Qu et al.[8], which included 8 studies, the authors evaluated 80 patients with dry-type OAB and 102 patients with wet-type OAB. Patients with wet-type OAB symptom had significantly higher urine NGF levels than patients with dry-type OAB (95 confidence interval=0.25–0.77, p<0.00001).

Antimuscarinic drugs (oxybutynin, tolterodine, trospium, fesoterodine, darifenacin, propiverin, and solifenacin) are the most commonly used medical agents in the treatment of OAB. In a study by Kim et al. [9], 62 patients with OAB were tested for urine NGF levels and antimuscarinic agents were prescribed for 4 months. It was found that the urine NGF levels decreased at the end of the 4 months (urine NGF/Creatinine (NGF/Cr) levels: 1.13±0.08 pg/mg; 16 weeks: 0.60±0.4 pg/mg; p=0.02). A trial by Hsin-Tzu et al.[10] showed that 34 patients, who were refractory to antimuscarinic therapy, had significantly higher urine NGF levels than the control group (0.0728 pg/mL versus 0–0.234, p<0.001) and after antimuscarinic treatment for 3 months, the urine NGF levels showed no change. In a study by Antunes-Lopes et al.[11], which included 40 healthy volunteers and 37 patients with OAB, the authors found that urine NGF/Cr ratios in patients with OAB decreased from 488.5±591.8 to 319.7±332.3 (p=0.008) after 3 months of lifestyle modifications and antimuscarinic treatment. In this study, the NGF levels were significantly lower in patients who received antimuscarinic therapy than in those who received onaBoNT-A injection (45.86±16.35 pg/mL versus 28.78±12.64 pg/mL, respectively; p=0.002).

OnaBoNT-A injection is frequently administered into the detrusor muscle in patients, including the administration of 2 different antimuscarinic agents and/or mirabegron for the last 3 months. In this study, 20 naive patients were treated with antimuscarinic agent and the other the 20 patients received onaBoNT-A injections. According to the questionnaire forms, patients in both the groups showed improvement at the 3rd and 6th month follow-ups compared with before treatment. In addition, this improvement shown in the questionnaire forms (OAB-V8, UDI-6, and IIQ-7) was statistically similar in the groups receiving antimuscarinic treatment and onaBoNT-A injections. However, the NGF levels did not show a significant change over time in the onaBoNT-A group (p=0.069), whereas the antimuscarinic group showed significantly lower levels at the 3rd and 6th month follow-ups (p=0.004, p=0.007; respectively). The absence of statistically significant decrease in the urine NGF levels in the onaBoNT-A group, who were refractory to antimuscarinics, raised a suspicion that a different effect mechanism might have played a role. Antimuscarinic drugs interrupt the parasympathetic nerve impulses by competing with the neurotransmitter acetylcholine at muscarinic receptor sites, and these drugs operate primarily by antagonizing the post-junctional excitatory muscarinic receptors (M_2/M_3) in the detrusor.[12] However, the mechanism of botulinum toxin-A includes the inhibition of vesicular release of the neurotransmitters and the axonal expression of capsaicin and purinergic receptors in the suburothelium, as well as attenuation of central sensitization.[13]

In addition, in the antimuscarinic group, a significant strong positive correlation was found between the NGF levels and OAB-V8 and IIQ-7 scores at the 3rd month follow-up. There was a significant moderate positive correlation between the NGF levels and UDI-6 scores at the 3rd month follow-up. At the 6th month follow-up, there was a very strong positive correlation between the NGF levels and OAB-V8 scores and a strong correlation

between the NGF levels and IIQ-7 scores. In the onaBoNT-A group, there was no significant correlation between the NGF levels and other variables.

Bhide et al.[14] reported the results of 20 studies, including 143 patients with idiopathic detrusor overactivity and 100 patients with neurogenic detrusor overactivity, and compared them with a control group of 38 healthy individuals without lower urinary tract symptoms. Patients who did not benefit from antimuscarinic treatment received onaBoNT-A; and 100 IU onaBoNT-A injection was administered to 24 patients with idiopathic detrusor overactivity, and 200 IU onaBoNT-A injection was administered to 19 patients with neurogenic detrusor overactivity. The NGF/Cr ratios (before treatment and at the 3rd month follow-up) were compared with the ratios of the 38 individuals in the control group. The mean urinary NGF/Cr ratios before treatment were significantly higher in patients with idiopathic detrusor overactivity (1.44±2.66) and in patients with neurogenic detrusor overactivity (0.62±1.22) than in the 38 individuals in the control group (0.005±0.019). After the onaBoNT-A injection, the urinary NGF/Cr ratios decreased significantly in patients with idiopathic detrusor overactivity (0.07±0.12, p=0.025) and in patients with neurogenic detrusor overactivity (0.096±0.17, p=0.033).

An important point in this study was that although the basal NGF level before antimuscarinic treatment was 45.86±16.35, the basal NGF level before onaBoNT-A injection was 28.78±12.64. The NGF levels decreased to 29.56±11.82 in the 6th month after antimuscarinic therapy. These values in patients with refractory OAB made us query if NGF levels could be helpful offer a limit value in the diagnosis of refractory OAB. However, to reveal these values, trials with a large number of patients are needed. This could be a preliminary and promising study in the diagnosis of refractory OAB by measuring the NGF levels. In a study by Suh et al.[15], the authors evaluated 189 patients with OAB to investigate urine NGF as a biomarker of treatment efficacy and recurrence. They concluded that urinary NGF was a potential biomarker for predicting the outcome of antimuscarinic treatment in patients with OAB. In addition, the authors emphasized that urine NGF might provide useful information in deciding when to stop antimuscarinic treatment in responders. A study by Alkis et al.[16] aimed to define the urinary biomarkers, which could predict the severity of OAB and detect the patients who would benefit most from the treatment. The authors stated that urinary biomarkers had a role in the pathophysiology of OAB; however, they did not predict the patients who would benefit from the treatment and in whom antimuscarinics would be useless.

The main limitations of this study were the limited sample size and reduction in the number of patients who did not re-consult at the 6th month follow-up. Although all the patients consulted at the 3rd month follow-up, only 50% (n=10) of patients who received antimuscarinic therapy and 30% (n=6) of patients who received the onaBoNT-A injection presented for the 6th month follow-up. Therefore, our results need to be supported by randomized, controlled, and large sample trials.

In conclusion, although the NGF levels did not show a significant change over time in patients who underwent onaBoNT-A injection, they were found to be significantly lower at the 3rd and 6th month follow-ups in patients who received antimuscarinic treatment. At the same time, it was also suggested that the urine NGF level might be a good marker to evaluate the effectiveness of treatment of OAB in patients receiving antimuscarinic therapy because urinary NGF levels correlate with the symptom scores. This lack of correlation in onaBoNT-A injection could be a result of the differences in the mechanism of action.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University (decision no:2016/313).

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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