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Novel biomarkers of overactive bladder syndrome

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ABSTRACT

The social aspect of overactive bladder syndrome (OAB) and the lack of objective diagnostic methods for this syndrome have spurred research into its potential biomarkers which can constitute useful diagnostic tools, while also allowing the evaluation of the intensity of clinical symptoms and the efficacy of implemented pharmacotherapy in OAB patients. Due to the complex etiopathogenesis of this syndrome, the researchers are seeking biomarkers connected with inflammation or nerve growth. The aim of this review was to analyse the latest literature data regarding potential biomarkers in OAB. The most promising opportunities are connected with the diagnostic use of the nerve growth factor (NGF), the brain derived neurotrophic factor (BDNF), C-reactive protein (CRP), prostaglandins and cytokines. Despite the most promising results to date having been obtained with regards to neurotrophic factors, it seems that, at the moment, none of these meets the criteria for becoming an isolated OAB marker. It is also suggested that the combined use of several biomarkers will facilitate obtaining the appropriate level of specificity and selectivity to allow their use in clinical practice.

Key words: biomarker, overactive bladder, diagnosis

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INTRODUCTION

OAB is a social disease which affects more than 10% of adults. It is a symptom-based condition, defined as a syndrome characterised by the presence of urgency, with or without urge urinary incontinence, which is usually accompanied by frequency and nocturia, in the absence of proven pathologies. Urinary urgency is a subjective symptom reported by patients, which is considered essential for making an accurate diagnosis. At present, the basis of OAB diagnostics is constituted by medical interview and the analysis of bladder diaries. Thus, there is a great demand for developing objective testing which would become a useful diagnostic tool and allow the assessment of the intensity of observed clinical symptoms and the monitoring of treatment efficacy.

Attempts are made to identify a non-invasive, cost-effective, sensitive and specific biomarker which could be detected in biological samples, using a simple and repetitive method. Below is a short review of the potential OAB biomarkers and the possibilities of their application in clinical practice.

BDNF

BDNF plays an important role in the normal functioning of sensory neurons. It belongs to neurotrophic factors (including NGF, BDNF, NT3 NT4) and is secreted from the *urothelium*. It binds with TrkB receptors present in both the *urothelium* and the afferent fibres of the bladder. Furthermore, it has a trophic effect on nerve tissue, and plays an important role in nociceptive processes, at both the spinal cord and supra-spinal levels, and also in inflammatory processes. Its presence was detected in terminal endings of sensory fibres, which where the presence of CGRP and substance P is found. It is suggested that the expression of BDNF is modelled by NGF. Its synthesis is significantly

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increased in the case of spinal cord injuries and chronic cystitis. The results of preclinical trials have shown that the acute intrathecal (into the spine) administration of BDNF induces an increase in urinary frequency, an effect which was not observed in the case of chronic administration [1].

The secretion of BDNF is usually induced by an increase in NGF synthesis in an inflamed tissue. Since BDNF plays an important role in the etiopathogenesis of both pain and inflammation, the work was undertaken with the aim to evaluate its role in the etiopathogenesis of cystitis and OAB. It was found that chemically induced cystitis changed the properties of afferent fibres in the spinal cord and dorsal root ganglia. It is suggested that BDNF is responsible for these adaptive changes and neuronal plasticity. It has been proven that the expression of TrkB receptors was significantly increased in L_1, L_2, L_6 and S_1 dorsal-root ganglia in the case of acute cystitis induced by cyclophosphamide, but not in chronic cystitis cases. These studies have confirmed that the level of BDNF is much higher in animals with cyclophosphamide-induced bladder hyperactivity.

There are studies proving that BDNF sequestration has a positive effect on bladder function in cystitis. Importantly, BDNF sequestration does not affect the physiological micturition reflex, which proves that BDNF modulates bladder activity only in the case of its dysfunction. It has been noted that the BDNF/creatinine (pg/mg) ratio is low in healthy people and is independent of gender or the circumstances of sample collection. A very significant increase in BDNF has, in turn, been found in OAB patients, in particular in people with OAB wet. Interestingly, the level of BDNF is increased in people with depression, usually coexisting with OAB, which might suggest this is a common element in the etiopathogenesis of these two diseases. Thus, it seems that urinary BDNF can become a valuable biomarker in OAB diagnostics. It is particularly worth pointing out that the conducted comparative analysis of the receiver-operator characteristic curves of urinary NGF/creatinine and urinary BDNF/creatinine in OAB patients demonstrated that BDNF had a better area under the curve than NGF [2].

BDNF was also analysed in the context of its possible use in assessing the effectiveness of OAB treatment. As botulinum toxin displays analgesic effects, which result from the inhibition of nociceptive neurotransmission in the spinal cord and the prevention of neurogenic inflammation, it was verified whether its administration into the bladder triangle in patients with bladder pain syndrome could affect BDNF levels. It was found that neurotrophin concentrations significantly decreased after one month from the administration of neurotoxin, which proved to correlate with a drop in pain intensity on a visual analogue scale. The patients also noted a subjective improvement in terms of daytime frequency and nocturia, one and three months following the administration of the botulinum toxin. The BDNF level increased gradually to reach the baseline value six months after the administration of the neurotoxin. Another clinical study proved that BDNF/creatinine decreased as a result of treatment with cholinergic blocking agents. What is particularly interesting is that the drop in BDNF/creatinine correlated with a decrease in urinary urgency, which was not observed in the case of NGF/creatinine [3].

In general, the BDNF concentration in urine is relatively low irrespectively of the time of sample collection. It has been proved that the BDNF/creatinine level is significantly higher in OAB patients than in healthy individuals (980.3 ± 1,774.8 vs. 110.4 ± 159.5). Interestingly, after three-month treatment its level in the OAB group was significantly reduced (980.3 ± 1,774.8 vs. 399.5 ± 487). This decrease was accompanied by a reduction in clinical symptoms (Indevus Urgency Severity Scale scores 3.29 ± 0.59 vs. 3.18 ± 0.39). Thus, it seems that BDNF can become an acute biomarker of OAB treatment efficacy. The results of the conducted studies showed that BDNF proved superior to NGF in OAB diagnostics. An obstacle to adapting BDNF as an OAB biomarker is the lack of standardised data concerning its reference values in healthy people, and the lack of knowledge of the threshold value above which this biomarker would show sensitivity and specificity in OAB diagnostics [4].

CRP AND CYTOKINES

It seems that cytokines can become a useful biomarker in OAB diagnostics, as their level in biofluids shows a tendency to increase in inflammatory processes. The results of clinical trials have shown that the level of the soluble fraction of the CD40 ligand (sCD40L) and monocyte chemotactic protein-1 (MCP-1) was several times higher in the urine of OAB patients when compared with healthy controls. A significant difference between the groups was also found in relation to growth-related oncogene (GRO-*α*), epidermal growth factor (EGF), and macrophage inflammatory protein (MIP- 1*β*), IL-12p70/p40, IL-5, IL-10 and sIL-2R*α*. It was also proved that the level of cytokines (MCP1, TARC, PARC and Fas/TNFRSF6) was increased in OAB patients, to the statistically significant extent.

Given that CRP is a recognised acute-phase marker of inflammation, which is synthesised in the liver as a response to the factors secreted by macrophages and adipocytes, the studies were also undertaken to examine this protein in the context of using it as an OAB biomarker. The tests included patients with OAB wet and dry, comparing CRP levels in the urine, blood and bladder tissue with their counterparts in healthy controls. The CRP levels were higher in patients of both studied groups when compared with the control group. At the same time, it was noted that the blood serum CRP levels, although higher in OAB patients, failed to reach

the values usually observed in the case of inflammation. Interestingly, it was also found that the CRP level was statistically significantly higher in OAB wet patients than in the OAB dry group. At the same time, it was observed that urinary and bladder CRP levels were considerably lower than the serum CRP level [6].

Other trials revealed a correlation between serum-CRP levels and episodes of urgency in patients with benign prostatic hyperplasia. The patients who reported urgency symptoms had significantly higher CRP levels than healthy individuals. At the same time, intensified OAB symptoms were noted in people with CRP levels > 0.3 mg/dL than in those with CRP levels < 0.3 mg/dL. High serum CRP levels were also found in women with OAB, with statistically higher values noted in the OAB wet group when compared with female patients with bladder hypersensitivity, but without the urodynamic symptoms of detrusor overactivity. Interestingly, a correlation was found between an increase in CRP level and a drop in the maximum urinary flow rates. Higher values of the maximum urinary flow rate and the body mass index turned out to be two independent factors affecting the CRP level. It was also proven that a CRP level of 1–3 mg/L entailed an increase in the risk of OAB symptoms, which might suggest that the inflammatory process plays an important role in the etiopathogenesis of OAB [7].

It seems that due to the very low values of CRP present in the urine and bladder which are detectable only in specialist research centres, it will be difficult to develop a urinary assay to become commonly available and ready for use in everyday clinical practice in the nearest future. It is also of essence that CRP is not a characteristic marker of pathophisiological processes underlying OAB, but only a non-specific marker of inflammation. It seems that at present it has too poor sensitivity and selectivity to become an isolated biomarker of OAB. However, it can be useful when combined with other biomarkers such as NGF or BDNF. Such combinations might significantly increase its diagnostic value [8].

PROSTANOIDS

Prostanoids (PGs) have a modulating effect on the functioning of the lower urinary tract. They play an important role in maintaining the basal tone of the urinary bladder, and impact on the afferent nerves which supply it. PGs are synthesised in both the *urothelium* and the bladder detrusor. Their synthesis increases in response to the stimulation of bladder nerve endings, detrusor contraction, urothelial damage, or inflammation. Their effect on the micturition reflex includes the lowering of the threshold value of impulses necessary to generate detrusor contraction. Therefore, it seems that there might be a correlation between the PGs level and the intensification of symptoms reported by OAB patients [9].Prostaglandins increase the afferent impulsation of the voiding reflex, leading to the occurrence of OAB symptoms. It has been found that COX-2 blocking with the use of non-selective cyclooxygenase inhibitors (ketoprofenum or indometacinum) increases the voiding threshold and the functional bladder volume in patients with detrusor hyperreflexia. Despite the fact that the subjective symptoms of OAB are improved, those medications do not modulate the cystometric parameters characteristic of DO in urodynamic tests. Such urodynamic changes, in turn, have been found after the administration of flurbiprofen, which led to the reduction in urgency and an increase in voiding volume. Due to the negative impacts of COX-2 inhibitors on the cardiovascular system, it seems that an interesting treatment option can be not so much the effects on COX but rather the determination of receptors for prostanoids. These theories find confirmation in the results of trials in which the animals genetically devoid of the EP_1 receptor have not displayed DO symptoms after the instillation of the bladder with a solution containing prostaglandins [10].

Preclinical trials have shown that administration of PGs to the lumen of the urethra induces its relaxation, while intravesical instillation causes detrusor contraction. The results of the clinical trials conducted have proved that the PGE_2 and $PGF_{2\alpha}$ levels in the urine of OAB patients are considerably higher than in healthy people. A correlation has also been detected between the PGE_2 level in the urine and the maximum cystometric capacity, and the volume to first desire to void. Such a correlation was not observed in relation to NGF, $PGF_{2\alpha}$ and PGI_2. In turn, the intravesical administration of PGE_2 proved to lead to an increase in maximal volume pressure and a drop in the voided volume. There are also studies in which the authors did not find any significant differences in PGE_2 levels between OAB patients and the controls [11].

The role of PGs in OAB diagnostics remains controversial. According to some researchers, PGE_2 levels are superior to NGF in diagnosing OAB. Interestingly, it was proved that the PGE_2 and $PGF_{2\alpha}$ levels in patients with detrusor underactivity, which had been confirmed in urodynamic tests, were considerably lower when compared with the group displaying the signs of DO. The differences between the groups in terms of PGI_2 were not observed [12].

ATP (ADENOSINE TRIPHOSPHATE)

ATP is secreted by urothelium in response to bladder contraction. It has been demonstrated that stretch-activated ATP release is markedly increased in OAB patients and whenever a decrease in the extracellular pH level is induced by bladder hypoxia. ATP mediates detrusor contractions induced by adrenergic and cholinergic neurotransmissions [13]. An in vitro study has shown increased ATP secretion by urothelium cells and cholinergic nerve endings

in OAB patients. The ATP level is now being investigated as a potential OAB biomarker. Preliminary results revealed that urinary ATP was increased in OAB (wet and dry) patients, which correlates with a reduced first desire to void in urodynamic tests [14]. Importantly, its level decreased in patients positively responding to pharmacological treatment with antimuscarinics. It was also shown that the urinary ATP to urine creatinine levels (ATP/Cr) ratio was significantly higher in patients with OAB and DO features, compared with the control group. An increased ATP/Cr correlated with a decreased mean voided volume. The area under the curve was proportional to the increased ATP/Cr level, which suggests that it can be a very sensitive biomarker of OD in patients with OAB symptoms [15].

NGF

The NGF action mechanism is mediated by two types of receptor: TrkA — with high affinity to NGF, whose density increases in inflammatory processes, and p75 — with low affinity, whose high expression was found in the *urothelium* of the patients with OAB symptoms. Apart from its impact on the above-mentioned types of receptors, NGF also affects the functioning of potential-dependent sodium channels (Nav 1.8, SNS, PN3) as well as NK and $TRPV_1$ receptors [16].

The results of preclinical trials have confirmed that the intravesical instillation of NGF causes OAB, increasing afferent impulsation through a rise in $TRPV_1$ receptor expression. DO symptoms could be reversed by NGF-neutralising antibodies. Thus, the blocking of receptors to NGF seems to be an interesting option for OAB pharmacotherapy [17].

A number of studies confirmed a positive correlation between increased NGF and OAB or DO symptoms. Pre-clinical study results demonstrated that this neurotrophin is profusely secreted by urothelial cells and smooth muscle cells in the detrusor of animals with a hyperactive bladder. It was proved that the intravesical instillation of NGF led to reduced intercontraction intervals and bladder capacity, which was indirectly confirmed by observations involving a TrkA receptor antagonist, which reduced the increased contractile activity of the detrusor in animals with spinal cord injury and interstitial cystitis (IC) [18, 19]. Interestingly, TRPV1 knockout animals, when administered NGF, did not develop DO symptoms, which might suggest that TRPV1 is a downstream receptor for NGF [20].

Based on the results of the pre-clinical studies, it was hypothesised that increased NGF levels in urine could sensitise afferent fibres in the bladder and, as a result, lead to the development of DO. This claim was supported by the clinical study which proved urine NGF levels to be much higher in OAB, DO, BOO and IC patients, compared with healthy populations. In relation to OAB, these differences were particularly significant (11-fold). Interestingly, statistically significant differences in NGF levels were also found between OAB wet and OAB dry patients, and a positive correlation was established between urgency and urinary NGF levels. Patients with Indevus Urgency Severity Scale scores ≥ 3 had considerably higher average NGF levels than those with scores ≤ 2. The results of studies on NGF sensitivity and specificity are of special importance in terms of the application in clinical practice. Specifically, it was demonstrated that when OAB patients were diagnosed using the NGF/creatinine ratio, the specificity was 93.8 %, and the sensitivity 67.9% [21]. It is suggested that the cut-off value for this parameter should be > 200 pg/mg.

The impact of pharmacotherapy on NGF levels in patients with OAB was also analysed. Therapy employing cholinergic blocking agents produced a decrease in this neurotrophin corresponding to the reduction in USS scores, which returned to their initial values after pharmacotherapy was discontinued. Consistent results were produced when patients with neurogenic bladders were administered botulinum toxin. These observations could suggest that NGF might become more than just a useful marker for OAB diagnosis, but also prove applicable for assessing the efficacy of pharmacological treatment [22].

ULTRASOUND

In patients with bladder outlet obstruction (BOO), OAB diagnostics has used the ultrasound measurement of bladder wall thickness (BWT) or only detrusor thickness (DT). For both these parameters, the measurements proved to be significantly higher among OAB patients than in healthy controls. This might have been due to bladder hypertrophy induced by its excessive contractibility. Some studies showed that increased DT correlated with greater urgency reported by patients. BWT measurements were also taken using intravaginal ultrasound in patients with idiopathic DO. It was found that in 58.7% of the analysed patients the average BWT was above 5 mm, of whom as many as 94% exhibited urodynamic DO characteristics [23, 24]. Only in 1.6 % of the patients with DO symptoms, BWT was ≤ 3 mm. Based on the above-mentioned findings, it is proposed that a BWT of 5 mm should be considered the limit for ultrasound screening tests for OAB. A positive correlation has also been found between the presence of OAB symptoms and high BWT and DT. Furthermore, BWT measurement makes it possible to distinguish between patients with BOO and those with clinical symptoms of stress urinary incontinence, which has significant clinical implications, since it can be used as the basis for targeted therapy in specific patients. Interestingly, DWT levels were reduced following successful treatment with cholinergic blocking agents [25, 26].

A problem which hinders the widespread use of BWT and DT is the lack of standardised measurement proce-

dures for these parameters. It has not been unequivocally determined whether these should be measured on a full or empty bladder. If on a full bladder, then what should be the volume? The majority of facilities prefer an transvaginal procedure, but some practitioners advocate that these measurements be performed transperineally [27, 28].

Some studies have demonstrated that DT levels in OAB patients show considerable diversification, thus making the results statistically insignificant, despite the clear tendency towards increased BWT and DT in OAW wet populations. This might be due to the use of various USG scanners across different studies, and, consequently, the resolution of the produced images. It is believed that, in the future, DT can become a pathognomonic marker for DO. This claim is based on the assumption that involuntary isometric bladder contractions induce bladder hypertrophy, which translates into the ultrasound-measured thickness of its detrusor muscle. BWT and DT measurements are considered a more reliable DO marker than cystometric measurements, especially in relation to patients with BOO [29, 30].

SUMMARY

The clinical trials conducted have identified several potential OAB biomarkers, including nerve growth factor, brain derived neurotrophic factor, C-reactive protein, prostaglandins and cytokines. In terms of sensitivity, specificity, cost- and time-effectiveness, it seems that, when used together, these markers can have greater diagnostic value and applicability in everyday clinical practice.

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