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The use of botulinum toxin for the treatment of patients with overactive bladder

Zastosowanie toksyny botulinowej w leczeniu pacjentek z pęcherzem nadreaktywnym

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ABSTRACT
Overactive bladder affects 12–17% of the population, and mainly women, and its incidence increases with age. Diagnosis of this condition is based mainly on the patients' complaints. These symptoms significantly affect the quality of life of millions of patients, involving considerable social, psychological, professional, physical and sexual problems. The wide incidence of this condition makes it necessary to find new medical substances in order to effectively eliminate the symptoms. Neurotoxins are a group of medical drugs that hold great promise for the future. Botulinum toxin is currently being used to treat symptoms related to overactive bladder. It can constitute an appropriate therapeutic option, in particular with regard to patients for whom the use of standard anti-cholinergic drugs is unsatisfactory or leads to severe side effects. Numerous research studies confirm that botulinum toxin can be efficiently used in the treatment of overactive bladder. The properties of this neurotoxin allow selective deactivation of overactive muscles. The use of botulinum toxin can be a method of treatment that significantly improves patient quality of life.
Keywords: botulinum toxin; overactive bladder; urinary incontinence; quality of life.

ABSTRAKT
Pęcherz nadreaktywny dotyczy 12–17% populacji, głównie kobiet, a częstość zachorowań wzrasta z wiekiem. Rozpoznanie tego schorzenia opiera się głównie na występowaniu objawów zgłaszanych przez pacjentów. W znaczący sposób wpływają one na jakość życia milionów chorych. Są związane z występowaniem znacznych problemów społecznych, psychologicznych, zawodowych, fizycznych i seksualnych. Tak szerokie rozpowszechnienie tego schorzenia powoduje konieczność poszukiwania nowych substancji leczniczych w celu skutecznego zwalczania objawów choroby. Grupą leków, z którą wiąże się obecnie duże nadzieje na przyszłość, są neurotoksyny. W ostatnim czasie w leczeniu objawów związanych z nadreaktywnością pęcherza moczowego wykorzystuje się toksynę botulinową. Toksyna botulinowa może stanowić właściwą opcję terapeutyczną, szczególnie w odniesieniu do pacjentów, w przypadku których standardowo stosowane leki antycholinergiczne cechują się niewystarczającą efektywnością lub nasilonym objawami niepożądanymi. Liczne badania potwierdzają, że toksynę botulinową można efektywnie stosować w leczeniu pęcherza nadreaktywnego. Właściwości tej neurotoksyny stwarzają możliwość selektywnego wyłączania nadreaktywnych mięśni. Zastosowanie toksyny botulinowej może być metodą leczniczą znacząco wpływającą na poprawę jakości życia pacjentów.
Słowa kluczowe: toksyna botulinowa; pęcherz nadreaktywny; nietrzymanie moczu; jakość życia.

INTRODUCTION

Overactive bladder syndrome (OAB), according to the definition from the International Continence Society (ICS), is a multisymptom condition characterized by urinary urgency, with or without urinary incontinence, i.e. involuntary loss of urine following an urgent need to urinate [1]. Overactive bladder is diagnosed on the basis of such symptoms as a sudden urge to urinate, usually with higher frequency of daytime micturition and nocturia [2], in the absence of such pathologies as urinary tract infections, interstitial nephritis, bladder tumor, bladder calculi, or neurological diseases [3]. The definition formulated in such a manner allows for the diagnosis of this condition without an obligatory performance of urodynamic examination [4].

Diagnosis of OAB is based mainly on the patients' complaints [5]. These symptoms significantly affect quality of life of millions of patients. They are associated with considerable social, psychological, professional, physical and sexual problems. They can also contribute to developing depression.

Prevalence of overactive bladder syndrome

Overactive bladder syndrome affects 12–17% of the population, mainly women, and the incidence increases with age [6]. It is estimated that nearly 70% of women over 50 suffer from urinary incontinence. In almost a 1/3 of the women it is one of the symptoms of OAB [7]. The results of the National Overactive Bladder Evaluation (NOBLE) studies, involving 2700 women in the USA and published in 2003, showed a clear relationship between the prevalence of OAB and the ageing process [8].

In accordance with epidemiological studies carried out in 6 European countries (France, Germany, Italy, Spain, Sweden and the UK) involving 16,776 men and women, the average prevalence of OAB was as high as 16.6%. The incidence of symptoms increased with age – from 8.7% in women aged 40–44 to 31.3% in women over 75. On the basis of the extrapolation, it was calculated that in 6 European countries there are about 18 million people suffering from OAB [9].

The quality of life of patients with overactive bladder

Overactive bladder is a common condition whose symptoms may considerably reduce the quality of life. In a study carried out by Sako et al., the authors assessed the impact of overactive bladder symptoms on sexual function in Japanese women [10]. The results demonstrated that OAB symptoms significantly contributed to sexual dysfunction in these Japanese women. Another study (Seul, 2017) showed that in about 1/3 of OAB cases the greatest discomfort is related to urine leakage. Considerably reduced quality of life as well as an increased rate of depression and stress are found in patients with OAB compared with the patients who can hold their urine. In particular, it pertains to those patients who do not respond to pharmacological treatment [11]. Overactive bladder is a condition frequently affecting also children and is more likely to occur in girls. Similarly as in adults, it constitutes a major individual, family and social problem [12].

Overactive bladder syndrome treatment

The high prevalence of OAB syndrome leads to the necessity of seeking new medical substances in order to effectively treat the condition, to minimize the impact on patients' quality of life. Since 1970, the treatment of OAB symptoms has become more effective. At that time, initiation of the treatment with the use of oxybutynin, the 1st non-selective anticholinergic drug, was followed by the introduction of other products acting on muscarinic receptors of the urinary bladder [13]. The effectiveness of oxybutynin amounts to about 24%, however, the severity of side effects, i.e. dry mouth, constipation and other gastrointestinal symptoms, is the reason for which a significant percentage of patients gave up the therapy (up to about 80% during a year) [14].

One group of highly promising drugs are neurotoxins. Recently, botulinum toxin has been used in the treatment of symptoms related to OAB.

Botulinum toxin – effects and application in medicine

In the years 1817–1822, Justinus Kerner documented the symptoms associated with botulism. On 14th December 1987, 34 Belgian musicians suffered food poisoning from smoked ham, and 1 of them died. Leftovers of the ham and some organs from the deceased were sent to Emile van Ermengem, Professor of bacteriology at the University of Ghent. He found the toxin responsible for the poisoning and named it *Bacillus botulinum*. At the beginning of the 20th century, the word *Clostridium* (the shape of a spindle) replaced the word *Bacillus* (*Clostridium botulinum*). Later, during World War II, Carl Lamanna and Edward Schantz managed to isolate and purify the toxin in the U.S. Army laboratories. Schantz continued research on the toxin at the University of Wisconsin with Eric Johnson and other co-workers. In 1965, Drachman demonstrated paralysis and atrophy in chicken muscles following botulinum toxin injection. These findings encouraged Allan Scott, an ophthalmologist, to conduct further investigations. His pioneering research related to the treatment of strabismus with botulinum toxin led to the approval of the toxin to be used in various fields of medicine [15] – Table 1.

Botulinum toxin was soon recognized as one of the strongest biological toxins [16, 17]. It is produced by *Clostridium botulinum* bacteria. Depending on the strain of bacteria, 7 types of botulinum toxins can be distinguished, denoted by the subsequent letters A–G [18]. All types of botulinum toxin have a similar mechanism of action, but they differ in terms of their degree of toxicity. Two serotypes: A and B are mainly used in medicine.

Botulinum toxin A is 1 of 7 neurotoxins produced by the anaerobic bacteria *Clostridium botulinum* and is the most potent biological toxins known [19]. It causes muscle paralysis by blocking the release of acetylcholine from cholinergic nerves [20]. Botulinum neurotoxins (BoNT) are di-chain proteins comprised of an N-terminal zinc metalloprotease light chain (LC) and a C-terminal heavy chain (HC), which includes the translocation and receptor binding domains. The 2 chains are held together by a disulfide bond. The LC cleaves soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs). The cleavage of SNAREs inhibits the fusion of synaptic vesicles to the cell membrane and the subsequent release of acetylcholine, which results in flaccid paralysis. The LC controls the catalytic properties and the duration of BoNT action [21] – Figure 1.

In most cases, the application of botulinum toxin does not result in muscle paralysis, but in a decrease of excessive tension.

Botulinum toxin has relatively few side effects. On account of the local application of the drug, its systemic action is rare and is related to the diffusion of the drug from the place of application to the adjacent or distant muscles [22].

Botulinum toxin A was first injected in 1988 in rhabdosphincter in patients with spinal cord injury resulting in detrusor-sphincter dyssynergia [23]. It resulted in a neuromuscular block in the area of rhabdosphincter and significantly decreased

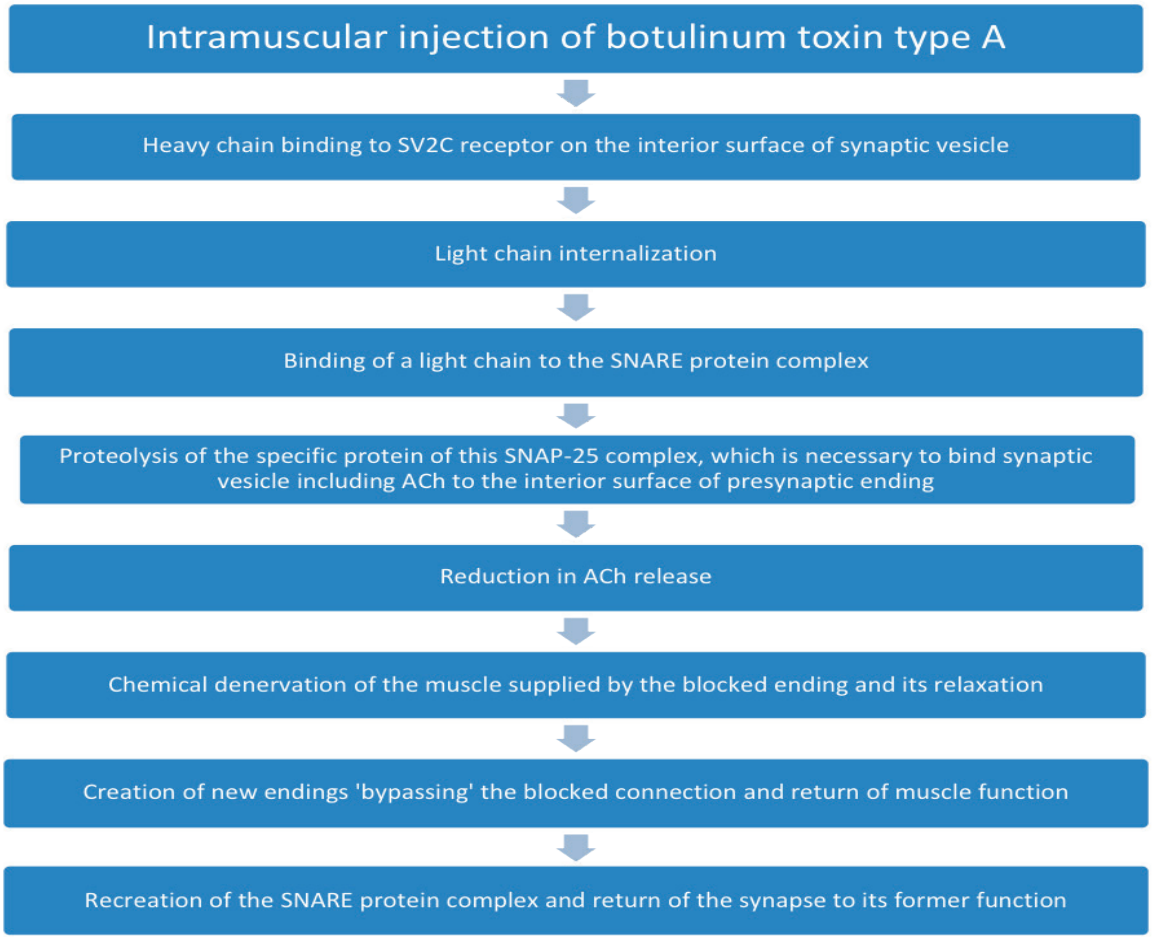
TABLE 1. The use of botulinum toxin A in medicine [16]

Field of medicine	Medical condition
Ophthalmology	different types of strabismus: strabismus concommitans, strabismus convergens esotropia, strabismus divergens exotropia, strabismus latens heterophoria, congenital, paraliticus, postoperative residual strabismus, convergence insufficiency; nystagmus and other acquired ocular motor disorders; excessive tearing; defective eyelid closure; intended temporary drooping of the upper eyelid; eyelid retraction; myokymia; spastic entropion
Neurology	dystonias: – focal: Meige's syndrome, oromandibular dystonia, tongue dystonia, bruxizm, spastic blepharospasm, cervical dystonia, throat dystonia, laryngeal dystonia, – segmental dystonias, – hemidystonia, – generalized dystonia, – symptomatic dystonias: Hallervorden–Spatz disease spasticity: – focal limb spasticity, – non-focal: hemispasticity, paraspsaasticity, tetraspasticity hemifacial spasm; synkineses after abnormal reinnervation; ticks; cerebral palsies; facial nerve paralysis and crocodile tears syndrome; synkinesis after idiopathic facial nerve paralysis hyperhidrosis: – focal: axillary, palmar, plantar, – generalized salivation: Parkinsonism, amyotrophic lateral sclerosis, muscle tremors pain: – muscle pain: caused by dystonias, spasticity, fibromyalgia, chronic facial muscle pain, chronic paraspinal muscles pain, – non-muscle pain: migraine, neuropathic pain, trigeminal neuralgia, phantom pain other: – Reynaud's phenomenon, – untreatable epileptic focal seizures
Urology	dissynergy of detrusor and sphincter muscles; idiopathic detrusor overactivity; neurogenic detrusor overactivity; urinary retention; bladder pain syndrome; pelvic floor muscles spasm; benign prostatic hyperplasia
Otolaryngology	gustatory sweating (Frey's syndrome); chronic rhinitis; laryngeal granulomas; glottic obstruction
Paediatrics	cerebral palsy
Gastroenterology	achalasia; cricopharyngeal spasm (inferior pharyngeal contrictor muscle); esophageal achalasia; pyloric stenosis; hirschprung's disease; sphincter of oddi spasm; gastroparesis; other: anal fissures, proctalgia fugax, anismus, obesity
Orthopaedics	dynamic clubfoot
Aesthetic medicine	glabellar wrinkles; wrinkles of inner eye corners

postvoid residual urine volume by allowing the urinary bladder to empty. Botulinum toxin can be a suitable therapeutic option, particularly for patients for whom conventional anticholinergic medication is insufficiently effective or leads to more serious side effects. Injections of botulinum solution into the bladder are performed during cystoscopy without the need for general anaesthesia. The fact that the therapeutic effect after a single injection may last even up to 9–12 months, and in some cases longer, constitutes a significant clinical advantage of botulinum toxin A. As a result, patients do not need to remember to take their medicines everyday [24].

Botulinum toxin as a method of overactive bladder syndrome treatment

Placebo-controlled trials confirm the long-term effects of botulinum toxin A. As a result, it started to be used in OAB treatment [25]. A study published in 2017 by the British Journal of Urology showed that 162 out of 195 patients with neurogenic detrusor overactivity experienced a ≥50% reduction in urinary incontinence following the botulinum toxin A treatment [26]. Injections into the bladder walls are highly efficacious in patients with OAB resistant to pharmacological treatment [27]. Patients need to receive repeated botulinum



ACh – acetylcholine

FIGURE 1. The sequence of events following the injection of botulinum toxin for muscle relaxation [22]

toxin injections after 5–9 months (but not earlier than after 3 months following its application) [28]. British Journal of Urology reports that the use of botulinum toxin A provides greater relief of OAB symptoms compared with most other drugs used in OAB treatment [29]. The Canadian Journal of Urology published the study demonstrating that botulinum toxin A is effective and efficient in OAB treatment [30].

In 2018, Einstein published the results of randomized studies carried out in Brazil, which indicate significantly better results of the botulinum toxin A injection than oral administration of oxybutynin in patients with neurogenic detrusor overactivity [31]. The Brazilian Journal of Infectious Diseases reported that an intravesical administration of botulinum toxin A reduced OAB with a long-term effect and improved the quality of life of HTLV-1 infected patients with severe overactive bladder [32]. The study conducted in Germany and published by Frontiers in Surgery showed that botulinum toxin therapy is an efficient, safe and life-improving treatment for patients with idiopathic overactive bladder [33]. Despite the fact that botulinum toxin has been successfully used for almost 40 years in various fields of medicine – ophthalmology, neurology, orthopaedics, laryngology and dentistry, it is still primarily associated with aesthetic medicine and so called beauty treatments [33].

CONCLUSION

Botulinum toxin can be successfully used in OAB treatment, which significantly improves the quality of life of patients suffering from the condition. Its properties allow selective deactivation of overactive muscles which cannot be achieved using other methods. However, further research is needed to identify all aspects of its action and the safe use of botulinum toxin in OAB treatment.

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