

P R A C E K A Z U I S T Y C Z N E
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Botulinum toxin – a new therapeutic agent in girls with non-neurogenic overactive bladder – a case report and review of the literature

Toksyna botulinowa – nowa metoda terapii u dziewcząt z nieneurogennym pęcherzem nadreaktywnym – prezentacja przypadku klinicznego i przegląd piśmiennictwa

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Abstract

The aim of this article is to present the safety and efficacy of intradetrusor botulinum toxin injections in the treatment of non-neurogenic overactive bladder in pediatric patients.

The electronic database MEDLINE (1966-2009) was searched including the following entries: non-neurogenic overactive bladder and botulinum overactive bladder. Data on the investigation topic are scarce.

Most of the papers concern neurogenic overactive bladder in adults, with only a few dealing with children with neurological disturbances. Therefore, the following paper presents a case of botulin toxin treatment in girl with overactive bladder. The patient did not tolerate the standard anticholinergic therapy and did not present neurological disturbances. Successful outcome allows us to state that intradetrusor botulinum toxin type A injection is a promising new treatment method in the refractory cases of non-neurogenic pediatric overactive bladder.

Key words: **non-neurogenic overactive bladder / botulinum toxin / therapy /**

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Streszczenie

Celem pracy była analiza bezpieczeństwa i skuteczności podawanej dopecherzowo toksyny botulinowej u dzieci z zespołem pęcherza nadreaktywnego o podłożu nieneurogennym.

Korzystając z bazy danych MEDLINE dokonano analizy piśmiennictwa opublikowanego w latach 1966-2009.

Wyszukiwanie artykułów przeprowadzono w oparciu o następujące terminy: *non-neurogenic overactive bladder*, *botulinum overactive bladder*.

Ogromna większość publikacji dotyczy zastosowania toksyny botulinowej u dorosłych lub dzieci z neurogenną postacią zespołu pęcherza nadreaktywnego. Zaskakująca jest niewielka liczba artykułów dotyczących zastosowania toksyny botulinowej u dzieci z nieneurogeną postacią zespołu pęcherza nadreaktywnego. Z tego względu praca została uzupełniona prezentacją przypadku skutecznej terapii toksyną botulinową u dziewczynki bez zaburzeń neurologicznych, zgłaszającej objawy pęcherza nadreaktywnego, jednak nie tolerującej terapii lekami o działaniu antycholinergicznym.

Key words: **nieneurogeny pęcherz nadreaktywny /
/ toksyna botulinowa / terapia /**

Introduction

Overactive bladder (OAB) is characterized by involuntary and unpredictable detrusor muscle contractions, causing an increased micturition frequency accompanied by a strong desire to void, leading to incontinence episodes in 30% of patients. The exact percentage of children suffering from these symptoms is currently not known but epidemiological studies in Europe and the United States show that this condition affects around 16.5% of adult population [1, 2]. Currently anticholinergics are the mainstay of OAB therapy but the tolerability of these agents is limited due to side-effects, such as dry mouth, dizziness, and somnolence [3]. Since bothering side-effects definitely could affect compliance, and, in the end efficacy of the treatment, there is a need for treatment modalities that both effectively control OAB symptoms and can be tolerated in the long term. There is also substantial group of patients who do not respond to anticholinergic therapy. Therefore, the solution for the nonresponders and patients with especially bothersome side effects may be intradetrusor botulinum toxin therapy.

For the first time effects of botulinum toxin ingestion were described in the late 1700s in Germany in cases of sausage poisoning. However, it was not until 1897 when this most potent biologic toxin was isolated from the anaerobic bacteria (*Clostridium botulinum*) by van Ermengem [4]. Of the seven distinctly isolated and structurally similar serotypes of botulinum toxin, only types A and B have been used in medicine. The product containing serotype A of botulinum toxin (BTX-A) is used in children and currently is becoming a standard in the treatment of spasticity secondary to cerebral palsy [5].

The activity of botulinum toxin within the neuromuscular junction has been described and consists of inhibition of acetylcholine release at the presynaptic level, resulting in striated muscle relaxation [6]. It does so by cleavage of the synaptosomal-associated protein with a molecular weight of 25 kD (SNAP-25), which physiologically is responsible for the docking of vesicles containing acetylcholine [7]. The lack of acetylcholine in synapse cleft results in suppressing of muscle contractility. In the urinary bladder botulinum toxin also appears to have an effect on specific sensory pathways, which may explain its efficacy in reducing urgency [8, 9].

Botulinum toxin has been found to inhibit the release of a number of other neurotransmitters such as, adenosine triphosphate, and neuropeptides: substance P, glutamate, protein kinase C and to down-regulate the expression of purinergic and capsaicin receptors on afferent neurons within the bladder wall [8, 10]. All these data support the view that botulinum toxin works in the detrusor overactivity and overactive bladder both, by sensory and motor pathways.

After introduction of botulinum toxin into treatment of detrusor overactivity in adults there is growing evidence that this regimen could be also efficacious in children. Further support for this strategy came from the case of 14-year old neurologically intact girl, noncompliant to the standard anticholinergic therapy.

Case report

Since early childhood our patient has been experiencing enuresis nocturna and symptoms of OAB with urinary incontinence. The diary showed 15 micturitions daily with volume from 12 to 25mls and first morning micturition with average volume of 110ml. The patient's siblings also presented urinary tract symptoms, the younger sister receives oxybutynin for OAB while the brother is treated with desmopressin for enuresis nocturna. Bladder sonography did not show residual urine, uroflowmetry results were within normal range. The patient was treated with oral oxybutynin chloride (5mg TID) and single evening dose of desmopressin (0.1mg). The response was excellent, patient noted total abatement of OAB symptoms and enuresis nocturna. However, after 2 months the girl became noncompliant, she stopped the therapy and all symptoms relapsed. Since the patient withdrew consent to oxybutynin chloride/desmopressin regimen, botulinum toxin was proposed instead. After obtaining an informed consent from the patient and her parents, 100 U of BTX-A (Botox) was given in 20 intradetrusor injections sparing trigone. The rigid cystoscope was used (diameter 9mm) and procedure was performed under short-time general anesthesia which, in our opinion, is obligatory in pediatric patients due to high level of anxiety. Initial response was good, we noted marked improvement of OAB symptoms during day. However, during the follow-up visit, 2 weeks later, the patient complained that all symptoms returned to the pretreatment severity.

The combination of oxybutynin chloride and desmopressin was started with good response but patient again stopped the treatment after a short time. We proposed another Botox therapy and 200 U was given in the same manner. Three months following the injection the girl remains dry and free of OAB symptoms but desmopressin treatment had to be started to control enuresis nocturna.

Discussion

Botulinum toxin type A has been used to treat a spectrum of neuromuscular and neuro-urological diseases. In urology BTX-A was first investigated in 1990 in the treatment of detrusor external sphincter dyssynergia in adult patients with spinal cord injury and currently also in idiopathic overactive bladder [11, 12, 13, 14]. Twelve years later Schulte-Baukloh et al. [15] reported the first study showing the effects of botulinum-A toxin in children with neurogenic detrusor overactivity.

Currently, in pediatric urological applications the two categories of botulinum toxin treatment are under clinical evaluation: the detrusor overactivity refractory to anticholinergics and voiding dysfunction. The use of BTX-A in the treatment of children with detrusor overactivity is definitely a second-line treatment option only when intolerance or failure after antimuscarinics occur. The main clinical goal is to improve urinary symptoms and quality of life. There is currently no consensus about the optimal treatment in children. Dosage, number and location of injections, type of cystoscope, and type of anesthesia should be verified in well, designed clinical trials.

The safety of intradetrusor injections in children is another issue. In animal studies the lethal dose of botulinum toxin was 39-40U/kg [16]. By extrapolation one can calculate that for an adult person weighing 70 kg the lethal dose will be as high as 2800U. In urogynecology usually a single dose doesn't exceed 300 U (50-300 U) and therefore it is very unusual that, such a dose, when properly applied, could really exert systemic effects. The most common symptoms after intradetrusor botulinum toxin injection are: detrusor areflexia with transient necessity of catheterization, increased post-void urine residual volume and spasticity of lower limbs [17, 18].

In our case we used 100 U of Botox, followed by injections of 200 U of the same medication. Our patient did not report any side effects related to this regimen. Good clinical response after second course of the treatment is particularly worth noting. We believe that that these positive effects could be related to combination of the two doses of BTX-A. Of course, it is far too early to establish of the treatment regimen in pediatric OAB refractory to the anticholinergic therapy. No real systemic side effects have been reported when the appropriate dose has been used [5]. Main contraindications to injection of botulinum toxin are: motoric neuropathy such as myasthenia gravis or Lambert-Eaton syndrome and also concomitant treatment with aminoglycosides.

Recently, Game et al. [19] presented a meta-analysis of six previously published studies concerning BTX-A use in children with neurogenic detrusor overactivity. In analyzed material the amount of injected BTX-A ranged from 5 to 12U/kg with a maximal dose of 360 U. The mean number of injection sites were 30 (range: 10-50), BTX-A was given in the bladder wall, sparing the trigone, under rigid cystoscopic guidance and under general anesthesia. Efficacy of treatment was measured in terms of

continence restoration and urodynamic findings. The mean reduction of urinary incontinence score varied from baseline between 40% and 80% but it should be pointed out that 65%-87% of children became completely continent. Statistically significant positive influence of BTX-A treatment on urodynamic variables were demonstrated in all analyzed studies. Botulinum toxin injection caused maximum detrusor pressure (Pdetmax) reduction in range from 33 to 55%.

Moreover, in most of the studies mean Pdetmax was reduced with BTX-A to <40cm H₂O, which is regarded as the desired value for upper urinary tract protection. The reduction in Pdetmax was accompanied by an increase in maximum cystometric capacity (MCC) varying, when comparing to baseline, between 110 to 200ml. From clinical point of view that was of critical importance because patients with a low mean MCC at baseline experienced a mean increase in MCC as high as 100-170%. In most studies authors noticed the improvement of urine continence and urodynamic parameters within 2 weeks after BTX-A injections and these positive effects persisted from 2 weeks up to 6 months [20].

Until now only one report was published concerning BTX-A treatment in children with non-neuropathic detrusor overactivity [21]. Study group consisted of 21 children (11 boys, 10 girls; aged 8-14 years) who were given 100IU of Botox, with 12 months follow-up in 15 patients. After first injection, 9 patients showed a full response as defined by the authors as no urgency and no urine leakage during the day. Additionally 3 patients showed a partial response (50% reduction in urgency and incontinent episodes) of which one responded well after repeat injection. Three children showed no response at all. The MCC was shown to have increased from 167 to 271ml. Eight children out of 15 maintained a response at 1 year, which is longer than usually observed among adult patients.

Conclusions

The evidence supports the use of BTX-A as a safe and efficacious treatment in children with detrusor overactivity and voiding dysfunction refractory to anticholinergics. Studies have demonstrated that BTX-A has long-lasting and beneficial effect on urinary symptoms, urodynamic parameters and children quality of life.

However, it should be pointed out that data on pediatric use of botulinum toxin is limited by the lack of controlled studies and the fact that most of the studies involved small numbers of individuals.

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