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Botulinum toxin type A in the treatment of laryngeal dystonia: a single-center experience

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ABSTRACT

Aim. The aim of this study was the analysis of the problem of laryngeal dystonia in patients of Otolaryngology and Neurology Clinics to assess the efficiency of effects of Botulin Toxin type A (BOTOX™) injections on voice quality and function of vocal cords with the use of videolaryngostroboscopic and laryngographic examinations, GRBAS (G - grade of hoarseness, R - roughness, B - breathiness, A – aesthenia, S -strain) scale and voice field.

Material and methods. Between 2020 and 2022 a total of 50 patients with laryngeal dystonia were examined. The videolaryngostroboscopic and laryngographic examinations confirmed laryngeal dystonia. Afterwards the patients undertook Botulinum Toxin type A injections into the thyro-arythenoid muscle.

Results. Control examinations confirmed the improvement of vocal folds movability and the decrease in number of irregular vocal folds vibrations. The next injection of BOTOX™ substance was done 3-6 months after the last injection.

Conclusions. The results of our study suggest that although BOTOX™ toxin still remains the main form of treatment for laryngeal dystonia, using it improves phonatory function of larynx (as proven by videolaryngostroboscopic examination).

Introduction

Laryngeal dystonia is a motor dysfunction of laryngeal muscles (1). It is a rarely diagnosed disease, although the first mentions about it came from 1911 when Oppenheim has described the symptoms of variable muscle tension in 4 of his patients and has named it as ''dystonia musculorum deformans". Subsequently Flatten and Sterling (31) introduced a different name of this illness- now introduced as ''progressing torsion spasm". Finally in 1984 the current definition of dystonia was created. It reads as follows: ''laryngeal dystonia is a symptom complex consisting of persisting agonist and antagonist laryngeal muscles, which in w zajętych parts of body cause repeatable and torsional movements. In effect it leads to an abnormal position of group of muscles or even the whole organ against each other or other parts of body." Moreover, the definition of dystonia was modified in XXI century by additng two axis: one focusing on characteristics of clinical feautures and an axis describing the etiology of the disease. These 2 axis decribe the clinical distinguishing features and the strict description of disease's etiology. The modern evaluation and definition of dystonia came as the effect of experience of veterinary medicine, where mutation-caused dystonia-specific brain changes were observed in animals during clinical tests It is belived nowadays that dystonia can be divided into two subgroups due to the etiology: primary (with disorders located in the central nervous system area- can be inherited or acquired) and idiopathic (of unknown cause which occurs not only sporadically but also sometimes is family-related). (2) In primary dystonia the absence of changes in diagnostic imagining (magnetic rezonance, computed tomography) is observed, as well as the ability of nervous system to morphological and biochemical change of neural pathways in response to environmental factors (1). Group of secondary dystonia consists of dystonia plus syndromes, dystonia in the course of degenerative diseases and Parkinson-related dystonia. Dystonia plus syndromes are not related to neurodegenerative diseases, it is worth to point out that other symptoms may be present e.g. ataxia, myoclonus (12)

Dystonia can be classified due to the location into generic dystonia, hemidystonia, segmental dystonia, focal and multifocal dystonia. Focal dystonia of laryngal muscles is rarely diagnosed and it is estimated that it occurs in 1-5,9 / 100 000 inhabitants of the Federal Republic of Germany (4). Currently there is no epidemiological data regarding the occurence of this disease in the territory of Poland. In animals the dystonia is less often diagnosed than in humans. There are some reports of generalized involuntary muscles contractions of unknown etiology in horses, which were discovered in 1910 (5). It is suspected that this disease is analogical to dystonia occuring in humans. Focal dystonia is revealed during implementing specific tasks (as so called task-oriented dystonia), in stress situations or as a result of external stimulus f.e.x light or noise. In humans the laryngeal dystonia is the 3rd most common primary focal dystonia. It occurs more often in women and the early onset of the disease is between 40-50 years old patients. Moreover in 12% the positive family history is confirmed. Most often it occurs in isolated form but in some percentage of patients it occurs in muscles of distant organs. (4, 6). Due to the unknown etiology the risk factors were introduced, which include age more than 40-50 years and positive family history, as well as different forms of stress, chronic inflammations of upper respiratory tract, intensive voice usage, torticollis, late pregnancy and confinement (7).

Koufman divides laryngeal dystonia into 4 main types on the basis of localization of pathological muscle movements (24):

- adductive,
- abductive,
- mixed,
- respiratory.

The most common type of laryngeal dystonia is adductor dystonia – in almost 80% of all patients with this disease. It can be divided into glottic type (when only muscle work is abnormal) and supraglottic type (when abnormal work of vestibular folds and supraglottic muscles are abnormal, as well as tremor of voice is observed). In case of mixed type the division relies on determination of the dominant pathology (abnormal adduction or abduction). Respiratory type is the most rare. The most characteristic feauture for this type are irregular vibations in laryngeal, pharyngeal and palatal muscles present during breathing (which are not present during speak-

ing and sleep). Due to the paradoxal movements of vocal folds stridor occurs as well as abnormal breaks during breathing (8,10, 9).

Aim

The aim of this study was the analysis of the problem of laryngeal dystonia in patients of Otolaryngology and Neurology Clinics of Cracow. The study focued on the assesment of the efficiency of effects of Botulinum Toxin type A injections on voice quality and function of vocal cords with the use of videolaryngostroboscopic examination, laryngography, GRBAS scale and voice field based on the experience of Otolaryngology and Neurology Clinics of the Universty Hospital of Cracow. We also compared our experience with other clinics.

Material and methods

Between 2020 and 2022 a total of 50 patients (46 women and 4 men) with symptoms of laryngeal dystonia have been treated in Otolaryngology and Neurology Clinics of Collegium Medicum of Jagiellonian University in Cracow, Poland. The mean age of examined patients was 67 years (median 76 years), while the youngest patient was 23 years old and the oldest was 89 years old. The medical diagnosis was made after comprehensive neurological examinations, excluding other diseases (e.g. miastenia) and after confirmation in laryngological and phoniatric examination. All patients were qualified for present study. In otolaryngological and phoniatric analysis the GRBAS scale (32) was used for subjective voice evaluation, voice field for sound ''a" was done and the videolaryngostroboscopic and laryngographic examinations were performed. This includes 5 components:

- **G** (grade – an overall grade of hoarseness),
- **R** (roughness),
- **B** (breathiness),
- **A** (aesthenia – weakness),
- **S** (strain).

Each component is rated on four point scale (**0** - normal, **1** - slight, **2** - moderate,and **3** – severe). The parameters of GRBAS scale were used for description of characteristic features of dystonic voice, obtaining the voice field enabled the graphical representation of dependence of individual tones from frequency range to intensity (from minimal to maximal intensity with witch they are created) (25), videolaryngostroboscopic examination was performed in order to asses the local condition as well as the movements of the vocal folds – the mobility and regularity of vocal cords were assesed. The last examination (the laryngography) was used to determinate the percentage share of irregular vocal folds vibrations (expressed as CFx - vocal folds irregularity coefficient). Typically in healthy patients CFx results should be lower than 10-12%; which corresponds to insignificant irregular vocal folds vibrations. In most of the examined patients the adductive type of dystonia was found (45 patients), while the respiratory type occured in 4 patients and 1 patient presented mixed type of dystonia. In every patient of this study botulinum toxin type-A (BOTOX^{tm}) injections into thyro-arytenoid muscle (through cricothyroid membrane) were used as a treatment. It was decided that every first injection will be done on the right side, while the following injections will be done by turns. All injections were guided by the EMG (electromiography) device. Moreover, every participant of the study was informed about possible side effects of botulinum toxin A (e.g. dyspnea). In case of occurence of acute shortness of breath there is a risk of urgent action in form of intubation or performing either the cricothyroidotomy or treacheotomy. After being informed about aboutsaid risks patients with mixed and respiratory types of dystonia refused the constent to treatment with BOTOX^{tm} and as a result this material was not included in this study. The dose of 7.5 units of BOTOX^{tm} was applied to each side which is in line with other studies. The follow-up examinations (otolaryngological-phoniatric) were done respectively 4 and 12 weeks after end of treatment with botululinum toxin. Besides phoniatric-neurological care the patients undertook neurologopedic rehabilitaion (e.g. lax-vox exercises).

Results and analysis

Before the study we observed the high values of R and S parameters of the GRBAS scale. In the analysis the values of G parameter were elevat-

Figure 1. The patient 4 weeks after injection of botulinum toxin type into the right vocal fold area (phonatory position)

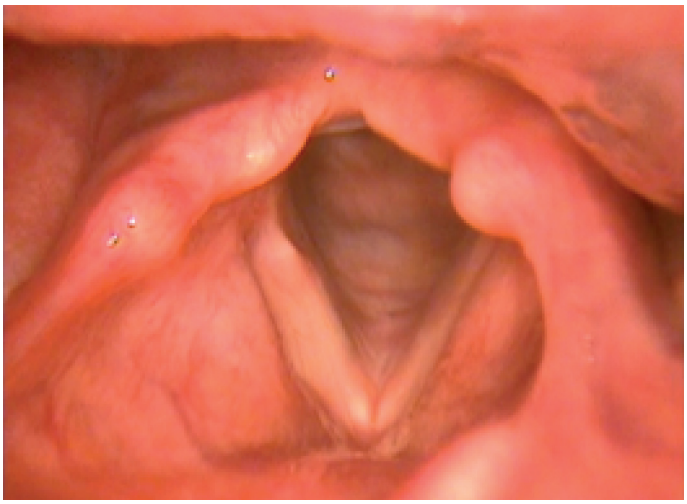

Figure 2. The patient 4 weeks after injection of botulinum toxin type into the right vocal fold area (respiratory position)

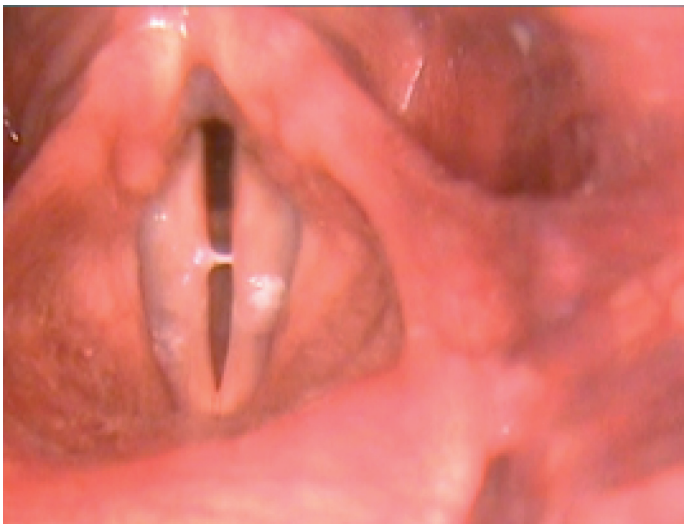

Figure 3. Patient qualified for botulinum toxin type A treatment (inspiratory phase)

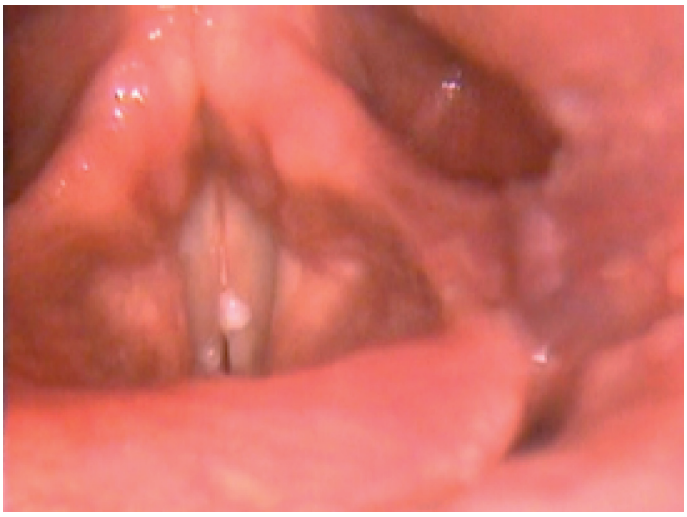

Figure 4. Patient qualified for botulinum toxin type A treatment (phonatory phase)

ed to 1 (22 patients; 48,89%) and 2 (23 patients, 51,11%) in all patients, while the values of R and S parameters were in most cases 3 or in selected cases 2 (e.g. the value of S parameter was as follows: 2 – 17 patients; 37,78% and 3 – 28 patients; 62,22%). The results translates into followings: 0 – *normal, physiological voice*, 1 – *mild changes of voice*; 2 – *average changes of voice*; 3 – *major changes of voice, very severe*. The improvement in movability of vocal folds in terms of regularity of vibrations and phonatory contraction was observed in GRBAS scale results (with simultaneous decrease of hyperfunction of vestibular folds); e.g. in case of G parameter after the therapy the results were as follows: 0 – 10 patients; 22,22%, 1 - 57,78% and 2 – 9 patients; 20%. These results correspond to the observations in the control videolaryngostroboscopy, where in all patients an improvement in mobility and regularity of vocal cords movements was observed. In

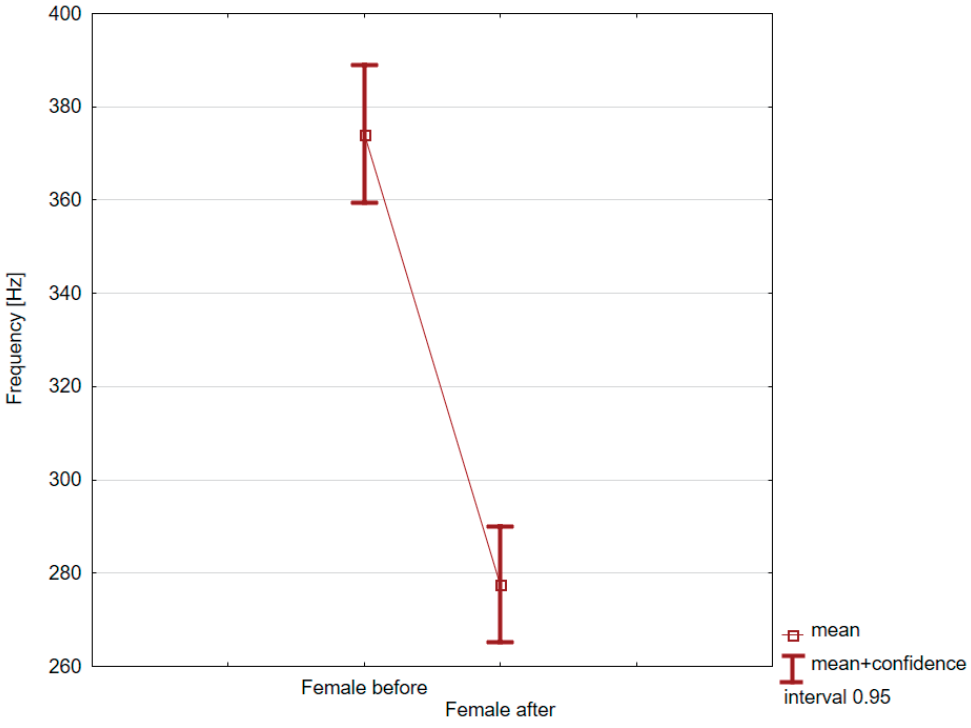

Figure 5. The change of Fmean in female population before and after BOTOXtm treatment (p=0.05).

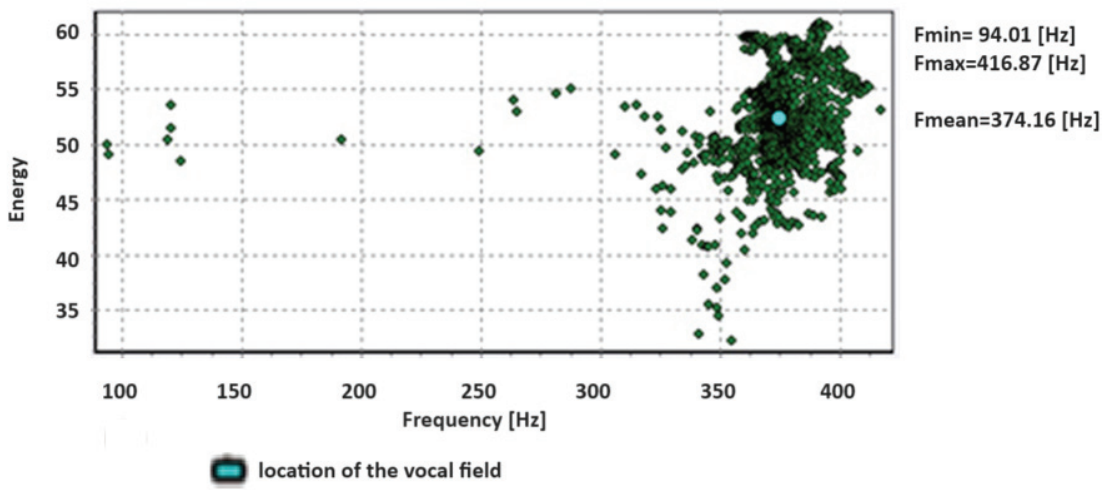

Figure 6. Average results of voice field measurement in females before botulinum toxin type A injection (Hz- frequency; lower bar – the location of the voice field)

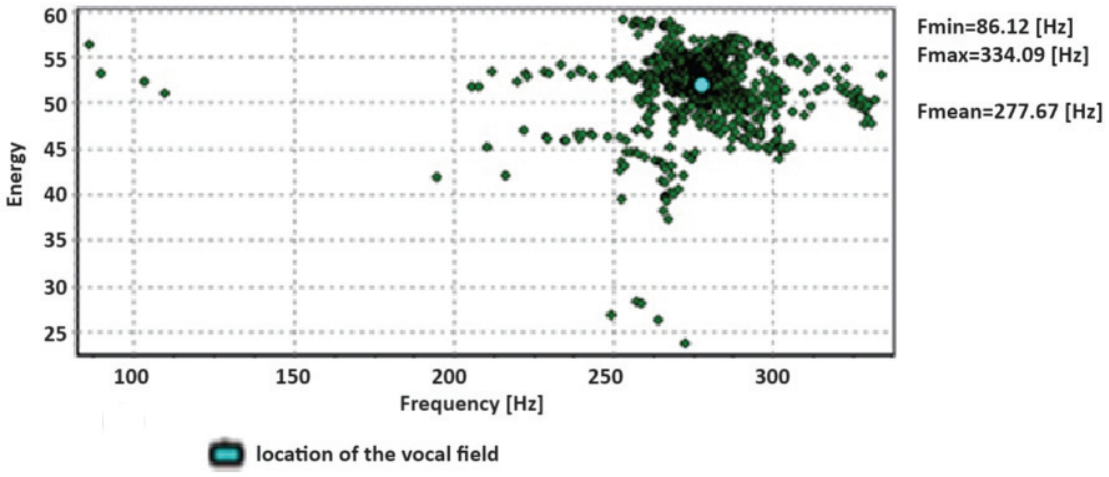

Figure 7. Average result of voice field measurement in females after botulinum toxin type A injection (Hz- frequency; lower bar – the location of the voice field)

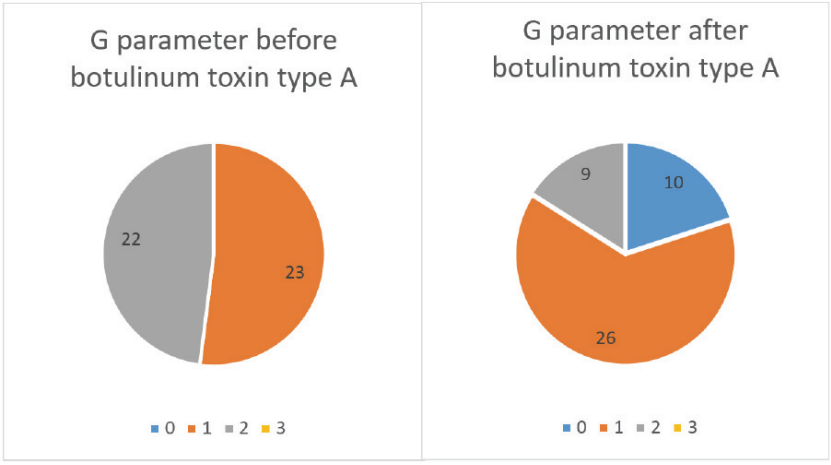

Figure 8. Pie graph showing the distribution of values of G parameter (0-3) of GRBAS scale among examined group of patients before and after botulinum toxin type A injection.

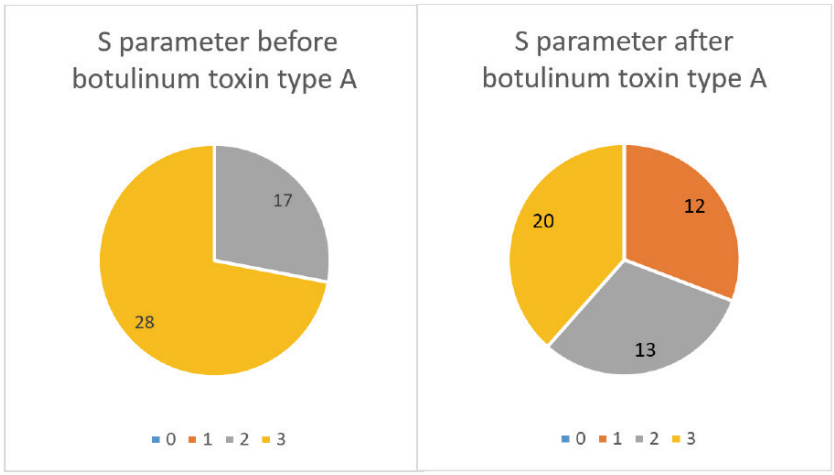

Figure 9. Pie graph showing the distribution of values of S parameter (0-3) of GRBAS scale among examined group of patients before and after botulinum toxin type A injection.

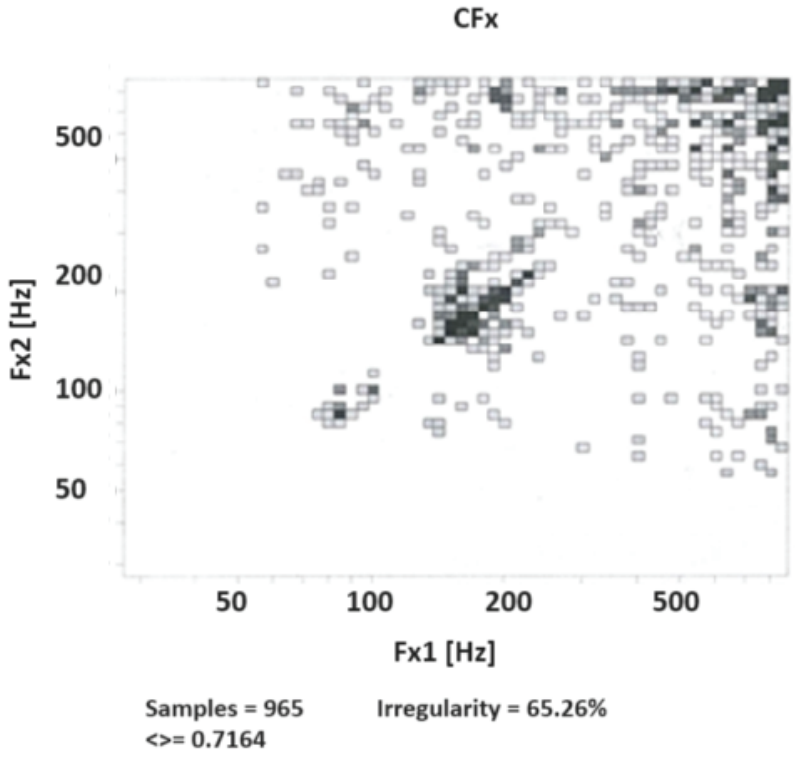

Figure 10. CFx control histogram before botulinum toxin type A therapy with coefficient of irregularity of vocal folds vibrations = 65,26% (p=0.05)

videolaryngostroboscopy before the study the irregular vocal folds vibrations with low mobility were observed in all patients, as well features of as so-called "laryngeal stuttering". The observations in case of this examination may be subjective (depending on the experience of the clinician); due to this fact other controls were performed (e.g. GRBAS scale or laryngographic examination). Before the injection of BOTOX^{tm} the average values for men were as follow: Fmin = 41,50 Hz, Fmax = 806,40 Hz and Fmean = 150,19 Hz, while for females were as follow: Fmin=94,01 Hz, Fmax = 416,87 Hz and Fmean = 374,16 Hz. After the therapy with botulinum toxin type A the following average results were obtained for Fmin, Fmax and Fmean, respectively: 58,98 Hz, 505,63 Hz and 143,00 Hz in males and 86,12 Hz, 334,12 Hz and 277,67 Hz in females. Despite observed algebra-

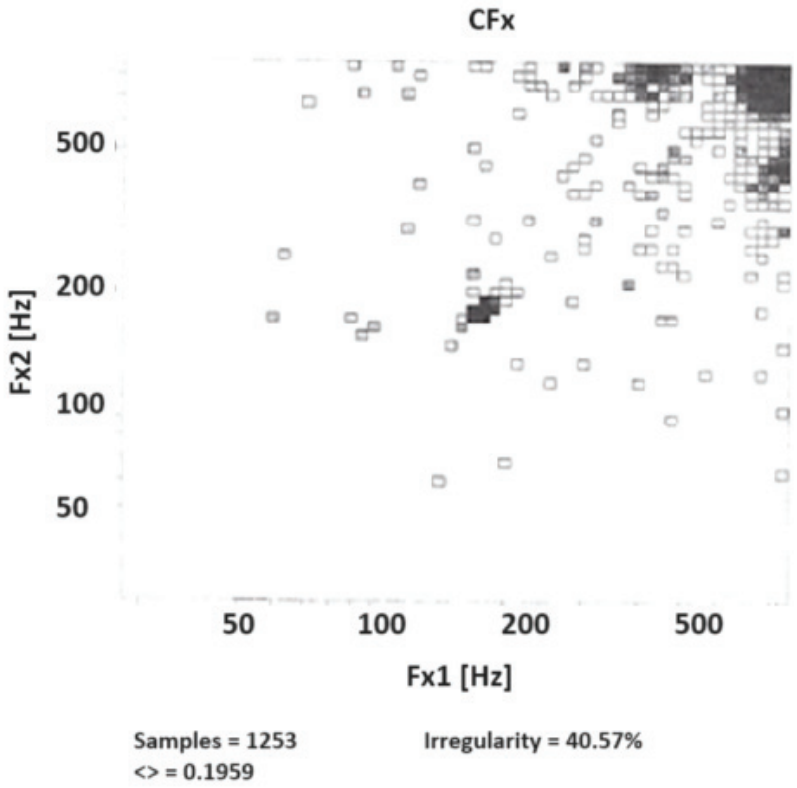

Figure 11. CFx control histogram 4 weeks after the end of botulinum toxin type A therapy with coefficient of irregularity of vocal folds vibrations = 40,57%. (p=0.05)

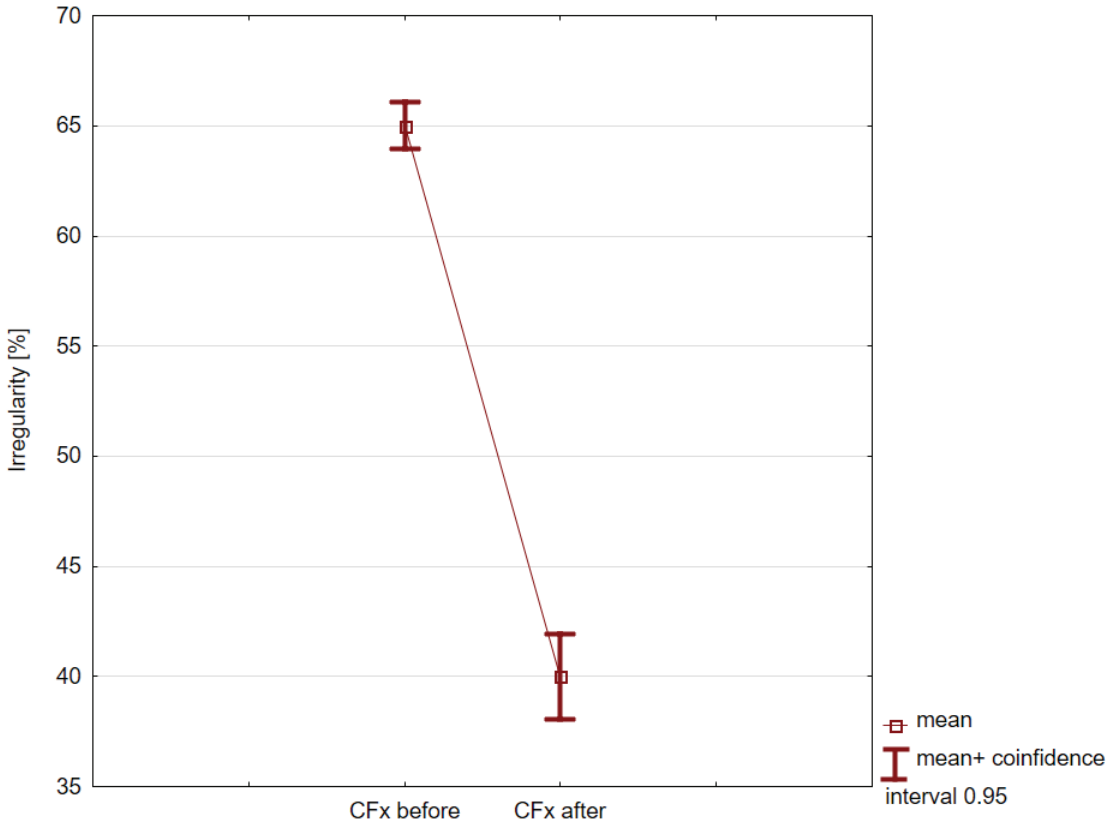

Figure 12. The comparison of irregularity values before and after the BOTOXtm treatment (p=0.05).

ic changes no statistically significant changes were detected in change of Fmean parameter for 2 populations (p=0.05). The high dispersion of measurement value for each patient versus mean value may be the reason behind such results. Therefore it may be challenging to obtain the statistically significant results. The next study should focus on bigger number of patients.

Nevertheless we observed that the change of Fmean in females is bigger than in males. Moreover there is a significant statistical relationship between the decrease of Fmean value (p=0.05) and the clinical improvement of laryngeal function after BOTOX^{tm} administration. The changes of Fmean results for female population were presented in Fig5.

In laryngographic control examinations (performed approximately 4 weeks after the end of therapy) we observed the decrease of value of CFx coefficient to about 45±5% from initial value of more than 60 % in all patients – mean 65±5 (Normal value of CFx should be between 0 and 10/12%) and the results were statistically significant (p=0.05) (Fig. 12).In addition, the lower the value of coefficient the bigger share of regular vocal folds vibrations in phonation process, what itself is the aim of the botulinum toxin therapy. In the following laryngographic examination, done 12 weeks after the first dose of toxin, the values of results increased slighty to CFx level of 50-58%. In case of voice field measurement after the toxin injection the decrease of minimal (Fmin), maximal (Fmax) as well as avarage (Fmean) voice frequency was observed.

The results suggested the stabilization of voice as a result of applied treatment. After 12 weeks the second injection of BOTOX^{tm} was applied into thyro-arytenoid muscles on the opposite site of the first iniection site. In control examination we obtained the similar results.

Discussion

Laryngeal dystonia is a serious neurological and otolaryngological problem and is still being explored and studied by clinicians from across the world. The described above symptoms of respiratory distorders with presence of paradoxal vocal folds vibrations are commonly observed. (30) Animal studies play a big part in an improvement of dystonia diagnostics. It is worth to obtain information about laryngeal dystonia based on animal models because of the similarity between anatomy of larynx in humans and other mammalian species. (18) Despite similarity in mentioned above anatomy and physiology of larynx, partial or complete paralysis of laryngeal muscles occurs more often in animals in comparison to humans (idiopatic paralysis of left recurrent laryngeal nerve in horses). The studies were also performed in dogs, in which laryngeal dystonia was induced after performing tracheotomy and connecting Harvard electrodes with recurrent laryngeal nerve (19). Stimulation of laryngeal muscles was used (cricothyroid and crico-arytenoid) and subsequently the impact of excessive muscles contraction on intraglottal pressure was investigated. Arytenoid cartilages were sustained in imposed, constant adduction as a result of this stimulation. The aim of these studies was to compare intraglottal pressure before and after stimulation of mentioned above muscles, which confirmed the impact of excessive muscle spasm on obtained results.

The current recommended method for laryngeal dystonia treatment (as well as for other focal dystonias) is the injection of botulinum toxin (BTX) into affected muscles (26). It is one of the strongest known neurotoxins of natural origin. Lethal dose for human is 0,2-2,0 μg/kg and is exposure-dependent (27). Gram-positive *Clostridium botulinum* is responsible for its production as a result of anaerobic fermentation (27). Currently there are 8 serotypes of botulinum toxin (A-H). The differences between them are as follows: molecular weight, antigenic structure, immunogenicity, receptors (and localisation of genes which are responsible for coding tchem) and half life time (27). In case of laryngeal dystonia type A of botulinum toxin was used, first in 1988 (28). Usually 2,5 units of botox are injected bilaterally or 5 units unilaterally. The effects of using the toxin appear about 3-7 days after the injection, when BTX binds with SV2C receptor and as a result SNARE protein is being blocked. Novakovich and associates (20, 27) report that even 28,5% of examined patients reported initial decrease of function of voice after administration of the toxin. Such effect is maintained for about 2 weeks, while during the next 6 weeks the normalization of voice occurs and the patient notices an

improvement in speech. After this time during the next 4 weeks the gradual worsening of phonation occurs. Moreover he reports that the disorders of phonation may be a result of f.ex wrong administration technique or drug dose. The resistance to botulinum toxin iniection is possible too. Marshall E. Smith and Charles N. Ford report 2 cases, where after long-term application of botulinum toxin the resistance to this substance and lack of effect after injection occured as a result. However, this phenomenon rarely occurs but in order to prevent it from happening the administration of the lowest effective dose and maintaining minimum 3 month-breaks between subsequent injections are advised. (33) The experience of University Hospital of Cracow in using botulinum neurotoxin is in line with other researchers as it prevails as the standard of care in LD, especially with a large body of evidence attesting to its efficacy. In Japan Hirose et al. demonstrated its therapeutic efficacy through a placebo-controlled, randomised, double-blind clinical trial. Botulinum Toxin therapy has been accepted and funded by the Japanese medical insurance scheme as a treatment for LD as a result of mentioned above study. Along with the work of Hyodo et al. (34) Dongren Yao et al. point that botulinum toxin injections are considered the first line of therapy of dystonia, with the highest use of botulinum toxin is reported in laryngeal dystonia and blepharospasm .(35) Moreover, Robert J. Stachler et al. in the United States recommend using botulinum toxin therapy along with regular laryngoscopy and prior to voice therapy in treatment of LD, what is in line with the experience of the Otolaryngology Clinic of Cracow. (36)

Currently there are no effective alternatives to therapy using injections of botulinum toxin type A. Berke and associates (21) have proposed surgical treatment of patients with adductive type of laryngeal dystonia. It is based on selective denervating and reinnervation of muscles responsible for adductive function of larynx - initially unilaterally, finally bilaterally. Even though the short-term results had brought hope for an improvment of phonatory function of larynx, the phonatory disorders returned in the long-term time. Thyroplasty type II is another surgical method and was introduced by Isshiki and associates (28). The aim of this method was prevention of excessive closure of glottis during phonation as a result of abnormal contractions. Failures of using above method in treatment of LD may be the result of difficulties in performing such type of surgery. Moreover, despite attempts with oral pharmacotherapy (e.g. anticholinergic drugs) no drug has been registered for laryngeal dystonia treatment. Pharmacotherapy itself is allowed as supportive therapy for treatment of patients with botulinum toxin type A. Speech therapy may play a role in treatment of laryngeal dystonia but currently there are no results of clinical studies confirming its effectiveness (22). Neurologopedic therapy can be an important part of the treatment due to the necessity of rehabilitation of communicative proces (which is disturbed to a large extent as a result of laryngeal dystonia).

Furthermore among new methods of treatment of laryngeal dystonia 2 groups are mentioned: central nervous system-focused methods and larynx-oriented therapies. First group includes e.g. deep brain stimulation. It is used in neurological disorders, like Parkinson disease; but in case of laryngeal dystonia using it requies special permisson. DEBUSSY (Thalamic Deep Brain Stimulation for Spasmodic Dysphonia) trial is an example of using deep brain stimulation in treatment of LD. In case of receiving positive results of the expermient this method may be used in patients with laryngeal dystonia. Second group consists of so called vibrostimulation of larynx and neuromodulation of larynx as a result of electrostimulation. The first of mentioned aboved methods is based on treating somatosensory dysfunction of the phonatory organ with usage of non-invasive vibrostimulation of lateral surfaces of thyroid cartilage (time duration: 40 minutes). In analysis after the stimulation the effect was mantained for about 20 minutes in 69% of examined patients. Currently studies are underway with aim of finding of optimal level of stimulation for obtaining the best effects of the treatment (29, 28). Neuromodulation of larynx is the second method. in the conducted study the stimulation of left thyroarytenoid muscles through hooked electrode was done. It was carried out for 5 days, 1 hour a day on a level lower than required for motor neuron activation. In 4 out of 5 patients the improvement in phonatory function was observed after the end of therapy and it lasted maximum of 14 days. Currently the new studies are underway with bigger number of examined patients. (28).

Conculsions

Laryngeal dystonia is an example of a disease, where the interdisciplinary cooperation is necessary. Videolaryngostroboscopic examination plays the key role in diagnostics of the disease. Non-invasive visualization of speech apparatus (phonatory) and determination of degree of voice disorders are both possible by using the laryngographic examination. GRBAS scale, as well as voice field measurement are another examples of useful, non-invasive phoniatric methods, which can be used to measure progress for both botulinum toxin type A therapy, as well as neurologopedic rehabilitation. The clinical results of our study suggest that botulinum toxin A injections improve phonatory function of the larynx, which provides an argument for its continuous use for layngeal dystonia.

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Authors contribution
Remigiusz Ziarno (conceptualization, data curation, formal analysis, project administration, writing – original draft); Małgorzata Dec-Ćwiek (data collection, analysis); Magdalena Sobuś (analysis, writing of the paper); Konrad Skórkiewicz (analysis, writing of the paper); Aleksandra Grudzień-Ziarno (analysis, writing of the paper); Jacek Składzień (data collection, analysis); Jerzy Tomik (data collection, writing of the paper, analysis)

Ethical standards
The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation (please name) and with the Helsinki Declaration of 1975, as revised in 2008 and assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guides.

Conflict of interest statement
The authors declare no conflict of interest.

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