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CERVICAL MUSCULAR DYSTONIA. MODERN APPROACHES TO TREATMENT

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ЦЕРВИКАЛЬНЫЕ МЫШЕЧНЫЕ ДИСТОНИИ. СОВРЕМЕННЫЕ ПОДХОДЫ К ЛЕЧЕНИЮ

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Cervical dystonia is a disease of the nervous system characterized by forcible discoordinated abnormal postures of the head and neck. There are several approaches to the treatment of dystonia: conservative drug treatment, botulinum therapy and neurosurgery. The latter includes deep brain stimulation, radiofrequency ablation, focused ultrasound, gamma knife. Literature data on this problem from open statistical and information databases such as Web of Science, PUBMED, Movement Disorders Society; International Association of Parkinsonism and Related Disorders were analyzed. Through a comparative approach, the advantages and disadvantages of modern approaches and interventions used in the treatment of cervical dystonia are noted. Among the modern methods of treating cervical dystonia, there are a large number of approaches that improve the methods of managing such patients. This review allowed us to summarize the experience of their application. A significant growth of abilities of stereotactic techniques used in the treatment of cervical dystonia was also noted.
Keywords. Cervical muscular dystonia, focused ultrasound, deep brain stimulation, radiofrequency ablation, gamma-knife, botulinum therapy.

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Цервикальная дистония – заболевание нервной системы, характеризуемое насильственными дискоординированными, патологическими позами головы и шеи. Поражая преимущественно трудоспособное население, заболевание приводит к социально-бытовой дезадаптации, что являет собой актуальную проблему. На сегодняшний день существует несколько подходов к лечению дистонии – консервативная фармакотерапия, ботулинотерапия и нейрохирургические вмешательства, такие как глубинная стимуляция головного мозга, радиочастотная абляция, фокусированный ультразвук, гамма-нож. Среди используемых подходов следует выделить наиболее эффективные тенденции, подходящие к условиям современного лечения дистоний.

Осуществлен анализ имеющейся литературы по исследуемой тематике из открытых статистических и информационных баз данных Web of Science, PUBMED, Movement Disorders Society; International Association of Parkinsonism and Related Disorders. Посредством компаративистского подхода отмечены преимущества и недостатки современных подходов и вмешательств, используемых при лечении цервикальных дистоний. Среди современных методов лечения цервикальных дистоний существует значительное количество подходов, совершенствующих методы помощи таким пациентам. Приведенный обзор позволил обобщить опыт их применения. Так же мы отметили существенный рост возможностей стереотаксических методик, используемых при лечении цервикальной дистонии.

Ключевые слова. Цервикальная мышечная дистония, фокусированный ультразвук, глубинная стимуляция мозга, радиочастотная абляция, гамма-нож, ботулинотерапия.

INTRODUCTION

Cervical dystonia (CD) – this is a common neurological syndrome characterized by involuntary contractions of the neck muscles, leading to violent, uncoordinated, twisting and repetitive movements with an unnatural pathological position of the head and neck, which is up to 50 % of all cases of focal dystonia (according to Mark S. LeDoux, S. Fahn [1]). Its prevalence in the population is up to 30–60 cases per 100,000 people [2]. The true pathogenetic mechanisms of the disease have not yet been clarified. A number of authors attribute a role to anomalies in the processes of inhibition, sensomotor integration, neural plasticity, and disorders in the functioning of calcium channels [3].

Clinically, cervical dystonia is classified according to the EFNS-MDS recommendations using the Western Toronto Spasmodic Torticollis Scale (TWISTRS) depending on the presence of exogenous or hereditary-degenerative genesis into acquired and idiopathic forms, respectively (the latter are associated with mutations in the loci of the DYT family of genes) [4]. Among the motor signs, postural and action patterns stand out, including dystonic positioning of the head and neck (torticollis, laterocollis, anterocollis, retrocollis, anterocaput, retrocaput, laterocaput, torticaput), dystonic tremor (usually action tremor that does not stop at the “zero point”). Among non-motor symptoms, anxiety-depressive disorders (48–53 % of patients, more among women), muscle pain syndrome (97.5 % of patients) were statistically significantly distinguished [5; 6]. Some authors also distinguish dyssomnia, cognitive and emotional disorders, emphasizing their primary implementation in the pathogenesis of dystonia [7]. Pathognomonic specific corrective gestures and movements (in-

cluding when imagining them) are a result of the inclusion of a sensory component in the pathogenesis [8; 9].

Treatment of dystonia initially consisted of physiotherapy and drug therapy, including central anticholinergic drug, muscle relaxants, benzodiazepines and levodopa. Oral medications are usually ineffective and have significant side effects, so today the gold standard of treatment is injections of chemodenervating botulinum toxins type A (BTA), classic examples of which are abobotulinumtoxin, incobotulinumtoxin and onabotulinumtoxin. The use of BTA medications showed a significant decrease in TWISTRS scores on average from –12.9 to –3.2 (at the 4th week and at the end of the cycle, respectively) with an injection frequency of 3–4 months [10; 11]. Their use in the treatment of spasticity, depression, headaches, and other conditions has also been described [12; 13]. According to the Cochrane review ($n = 1144$), when using botulinum toxins, the proven improvement in the baseline TWISTRS level (43.5 on average) ranges from 18.4 to 56 % (by the 4th week and by the end of use, respectively). It is summarized that the frequency of unsatisfactory results largely depends on the anatomical verification of the muscles affected by the dystonic pattern, the starting dose of the drug, the level of compliance, and the presence or absence of the titer of neutralizing antibodies.

Among the modern possible ways to improve the results of botulinum therapy, it is possible to note the use of a combined synergy of two methods – EMG assistance and ultrasound navigation (the so-called "double control" method), since up to 37 % of unsuccessful treatment cases depend on inaccurate verification of target muscles [14]. The technique allows to significantly reduce the frequency of trauma to the vascular-nervous bundles and increase the frequency of precise injections, which significantly increases the effectiveness of therapy [15; 16]. It has been established that the combination of the two techniques is more effective than each taken separately [17]. Also, experience of botulinum therapy using F18-FDG PET/CT navigation data ($n = 78$) with a positive response in 50 % of patients, a reduction in symptoms assessed using the TWISTRS Scale by more than 30 % (by 15.0 points, respectively) has been declared. The advantages of PET navigation have made it possible to predict the response to therapy by assessing the degree of hypermetabolism in muscles and visualize the deep muscles of the neck [18]. "Functional isotope navigation" has opened up prospects for performing targeted surgical interventions for selective denervation with myotomy in cases of dystonia refractory to botulinum therapy [19]. In a double-blind randomized trial ($n = 122$), the use of Tc99m-sestamibi SPECT also allowed identification of affected muscles with a sensitivity and specificity of 93.2 % and 88.5 %, respectively. It was shown that in the long-term period, visualization improved the

effectiveness with an assessment on the TWISTRS Scale to −4.86 (95 % CI from −9.40 to −0.32; $R = 0.036$) in patients, compared with the group where botulinum therapy was carried out in the classical way. The first documented experience of CT-assistance with improvement of long-term treatment results was given by Russian authors [20]. The problem of the absence of a pronounced effect in 20 % of patients is explained by W. Poewe et al. by the unequal effectiveness of different dosages (using placebo as an example), confirming the best results of high starting doses at the beginning of therapy, however, it is worth remembering the precedents of general reactions [21; 22]. In addition, methods of combining therapy with BTA drugs with venlafaxine are proposed, which correct pain syndrome and compliance to a greater extent and show positive treatment dynamics [23]. O.R. Orlova et al. noted that, in addition to the local synaptotropic effect of botulinum toxin, the reduction of non-motor symptoms, in particular pain syndrome, is associated with additional central afferent mechanisms mediated by retrograde axonal transport, which determines the effect on the sensomotor pathogenetic component at the segmental and suprasegmental level, which is confirmed by the data of Z.A. Zaljalova et al. [7; 24]. The use of venlafaxine appears to enhance these effects to a certain level, but the case of its induction of dystonic symptoms should be kept in mind [25]. It is known that from 39 to 83 % of patients during the treatment cycle experience a decrease in the effect of BTA and a return of symptoms on average at 10.5 weeks (with a 12-week cycle), which leads to a decrease in satisfaction with the results, low compliance and, as a consequence, refusal to continue therapy [26]. Thus, over time, control over the severity of the disease is lost, worsening its form. Works with a small number of observations on the different duration of the effect of different forms of BTA drugs have been published, which is important for choosing the time of the subsequent injection [27]. Several studies have noted that additional injections into the inferior oblique muscle may increase the subjective improvement in patients' quality of life [28]. It should be taken into account that non-motor symptoms such as chronic pain syndrome and anxiety-depressive disorders (aggravated by alcohol consumption), often accompanying CD, significantly affect the subjective perception of the effectiveness of botulinum therapy, for example, pessimistically assessing its results [4; 29].

Despite the effectiveness of botulinum therapy and significant experience in its use, some patients do not achieve stable control of the disease symptoms or develop individual refractoriness [30]. In addition, the treatment is not without significant drawbacks. These include the need for periodic injections (every 3–4 months), and unequal effectiveness in various forms of CD, such as anterocollis, retrocollis, and shift. Up to 46.5 % of patients refuse therapy due to the development of muscle weak-

ness, dysphagia, dry mouth and headache [31]. This leads to the consideration of neurosurgical interventions in the maintenance of patients with CD.

The first surgical operations, dating back to the 19th century, usually included posterior rhizotomy according to Foerster, unilateral or bilateral transection of motor or sensory roots, or decompression of the accessory nerve [32]. They were used only to a limited extent due to such known complications as high mortality and, at the same time, low efficiency. The experiments of W. Hess and R. Hassler, who used functional pallidotomy in the area of Forel's H1 field and thalamotomy in the projection of the ventrooral, ventrointermedial nuclei, and the internal nucleus of the globus pallidus (GPi), opened the era of stereotactic interventions in dystonia [33].

DEEP BRAIN STIMULATION (DBS)

This is deep brain stimulation – a currently widely used invasive implantation procedure for high-frequency chronic stimulation in focal, segmental, cervical and generalized dystonias. It involves the presence of a subcutaneous stimulator installed on the anterior chest wall, acting on the target of interest through inhibitory stimulation, as well as through action on A1-adenosine receptors, desynchronizing pathological impulses of nuclei, while allowing for correction of the supplied frequencies and partial control of the symptoms of the disease. Also, through the neuromodulatory effect, a local change in metabolism occurs, which has a therapeutic effect due to the influence on neuroplasticity processes. The main target for cervical dystonia is the pallidothalamic tract (PTT), the ventrointermediate nucleus (Vim) (in dystonic tremor) and ventrooral nucleus (Vo).

Retrospective studies conducted in 2012 described the analysis of positive responses after the DBS-GPi procedure for primary idiopathic segmental dystonia at 6 months, 3 and 5 years, respectively, in 83, 94 and 81 % of adult patients ($n = 40$) with a reduction in symptoms according to the Burke – Fahn – Marsden Dystonia Rating Scale (BFMDRS or BFM) by 54.5, 49.4 % [34]. The mentioned analysis also included data from a French multicenter study (Stimulation du Pallidum Interne dans la Dystonie, SPIDY) ($n = 31$). These included a corresponding response rate after surgery of 67 and 60 % at comparable 3- and 5-year examination and a regression of dystonia symptoms of 44.8 % in the first 6 months and 67.0 % by the end of long-term examination. Using the same scales, other authors obtained improvements in treatment results, assessed using quantitative scales by 69 and 79 %, respectively [35].

Studies comparing the outcomes of patients who underwent DBS intervention ($n = 102$) reported an improvement of at least 20 % from baseline in the motor portion of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) [36]. Studies comparing the outcomes of patients who underwent DBS intervention

(n = 102) reported an improvement of at least 20 % from baseline in the motor portion of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) [36]. In combination with the indicators of pain syndrome severity and the relative decrease in the severity of CD according to other subscales and the comparative evidence of effectiveness with DBS imitation, the results allow us to present this study as clinically successful. The complications from bilateral implantation reported by the authors include a smaller proportion of affected patients from the total number (36 %), but, among other things, are supplemented by postoperative stroke and hemiparesis. When comparatively analyzing the results of 24 non-conforming studies (n = 532) with patients of comparable age and duration of observation, it is possible to conclude that the intervention is effective, since a decrease in the median on the BFMDRS Scale by 58.6 % was noted after 6 months (with the greatest effect of 51.8 % in those operated on with primarily generalized and focal cervical forms) and 65.2 % after 3 years, respectively (40 and 70 % are similar for the TWSTRS Scale) [37]. The complications listed in the cited works included both correctable (electrode fracture, technical malfunctions) and other complications in the form of bleeding; however, it is necessary to take into account the comparatively smaller proportion of dysarthria and dysphagia when extrapolating their frequencies to the spectrum of pallidotomy complications. As in previous studies, the need for careful selection of patients was indicated, since there is a strong relationship between young age, onset and severity of the condition according to the analyzed scales. Recent analytical reviews on cervical dystonias highlight articles comparing the use of GPi and effects on the subthalamic (STN) nuclei. But if we compare the effectiveness of the operations (while extrapolating metadata to 2020) with the reduction of symptoms according to the Western Toronto Scale, then based on the data obtained in 59 and 60 %, we can conclude that they are equally effective. DBS has proven itself as a method that provides the ability to modify adjustable parameters individually for each patient with subsequent regulation of clinical symptoms over time. As a rule, the clinical phenotypes of laterocollis and torticollis are the most favorable in terms of response to stimulation, while retcollis and shift forms have a very controversial prognosis, since the above-mentioned works contain indications of complications occurring with a fairly high frequency.

The main disadvantages of DBS are the need for periodic replacement or recharging of the electrostimulator batteries depending on the value of the frequencies set, the need to select a stimulation program, the invasiveness of the procedure, the high cost of the necessary equipment and the installation of foreign implants, which do not exclude complications such as 0.4 % mortality. This causes a mixed attitude towards the results of this method among a number of authors.

RADIOFREQUENCY ABLATION (RFA)

This is a medical procedure that is a minimally invasive technique based on the transmission of radiofrequency alternating current using a needle probe into various anatomical structures with subsequent irreversible destruction. The essence of the method is to create a lesion by means of heat through an intracranial insulated electrode (except for the tip). The electric field between the two electrode contacts oscillates and causes nearby ions in the electrolyte medium to move back and forth in space with the same frequency. The tissues are heated by friction generated by the radiofrequency oscillations of the ions, which results in tissue heating and induces damage to the area of interest. The target structures for RFA operations are the ventroral, ventrointermediate nucleus, pallidothalamic tract and GPi. The results of treatment of patients with primary dystonia using RFA after unilateral pallidotomy and contralateral pallidothalamic tractotomy are presented, where the presented results in 6-month dynamics, assessed using the BFMDRS Scale, showed a reduction in symptoms by 88.6 % [38]. The authors summarized the decisive role of bilateral ablation, with a few exceptions such as laryngeal symptoms, citing the experience of previous studies with achieved results of reduction in BFMDRS scores after 6 months, 5 and 10 years by 70.5; 45.7 and 31.1 %, respectively. Cases of cervical dystonia have been described, the symptoms of which regressed along with pain syndrome in up to 90 %, while the need for other supportive therapy was completely eliminated [39]. Recently, several relevant CT-guided studies have been reported, one of which was cited as a successful treatment option with a symptom reduction assessed by the BFMDRS of 77.4 % [40].

However, when analyzing data from a few interventions, episodes of facial paresis are reported due to local impact on adjacent targets. Common complications of RFA include intracerebral hemorrhage, damage to nearby structures directly during the procedure, and a high risk of surgical infection. The RFA technique is an alternative for the treatment of cervical dystonia when DBS is contraindicated.

GAMMA KNIFE ABLATION (GKA)

It is a radiosurgical procedure using the isotope cobalt-60, which emits a known number of gamma radiation beams that converge on the target of interest with high precision. The technique uses ionizing radiation without the need for invasive electrodes, thereby reducing the risk of infectious complications. At the isocenter, the beams create a high total radiation dose, which is corrected by collimators and sectors of different sizes, ensuring high targeting accuracy using the Elekta system. The mechanism of ablation action consists of damaging the DNA of the target cell and creating a focus of radiation necrosis. This allowed

the method to be successfully applied in neuro-oncology. A relatively small number of cases of dystonia treatment using this approach have been published. However, a pooled review of the use of GKA in 16 patients was reported, of which only 30 % achieved significant improvement [41]. These results are not sufficient to recommend gamma knife therapy, but it may be an option in certain patient groups, particularly those with coagulopathies, cardiovascular disease, and the elderly.

Focused ultrasound under magnetic resonance guidance (MRgFUS)

The greatest emphasis today is placed on the use of focused ultrasound under magnetic resonance guidance (MRgFUS) – a technology for non-invasive ultrasound surgical intervention without the use of ionizing radiation and foreign implants. It allows the creation of a thermal ablation focus with a precision of up to 1 mm by focusing beams of high-intensity ultrasound energy under MR guidance through bone tissue, reaching deep-lying nuclei and structures, creating a thermal ablation and cavitation effect. This method involves a step-by-step effect on the selected area with subtherapeutic and therapeutic temperatures (45° and 55–60 °C, respectively, under the control of MR thermometry), the result of which is a formed zone of coagulation necrosis. Another feature of the method is the constant monitoring of the patient's symptoms, while the patient remains conscious throughout the entire operation.

Despite the small number of studies devoted to high-intensity ultrasound, a retrospective analysis of the treatment results of 13 patients with cervical dystonia was presented. The study reported a decrease in TWSTRS scores from 22 before treatment to 6 points after. In 4 patients, bilateral Vo-thalamotomy with PTT-tomy was used, while in the rest, depending on the dominant symptoms, one target or a combination was selected. Overall, 70.6 % improvement was achieved [42]. No serious complications related to the surgery were noted, except for one case of logorrhea and micrographia that regressed after three weeks. In 2017, a 6-month observance of three cured patients with cervical dystonia and dystonic tremor was reported [43]. The use of ultrasonic thermocoagulation of the Vim nucleus with Morel mapping resulted in a decrease in scores on the BFMDRS Scale from an average of 15.0 ± 3.0 to 8.0 ± 2.0 against the background of minor paresthesia of the lip, which regressed before the end of the study.

In addition to such contraindications to the operation as excessive thickness of the skull bones due to aberration of the rays and excessive heating of the tissues, there is a significant attachment mainly to the deep structures of the brain, since this reduces the accuracy of focusing. Another disadvantage worth mentioning is the small number of authorized centers involved in MRgFUS, due to the high cost of their initial establishment.

Conclusions

Dystonia remains a current problem that requires various treatment methods. The effectiveness of botulinum therapy undoubtedly depends on the accuracy of intramuscular injection, which has been greatly improved by various navigation and monitoring methods. Individual selection of dosages and injection cycles with correction of pain syndrome and emotional background of the patient allows to increase the level of compliance and, possibly, slow down the progression of cervical dystonia. The presence of a course of this form of dystonia that is refractory to botulinum therapy forces us to resort to a surgical array – from radiofrequency and gamma knife ablation, deep brain stimulation to the use of focused ultrasound. Among modern interventions, DBS occupies a strong position as the most studied invasive method with additional effects from the stimulation therapy produced with comparable results in the reduction of dystonic patterns. When comparing non-invasive techniques, the best results were achieved using MRgFUS, which was confirmed in studies showing greater efficiency and less positioning error than when using RFA. Imagine the small number of documented cases of treatment of cervical dystonia by the MRgFUS method, which is rather associated with a short period of clinical use due to the novelty of the technique. It is worth considering that, if there are indications, the use of GKA and RFA, which can be effective in certain groups of patients, is not excluded.

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