

MRI-Guided Focused Ultrasound in Cervical Dystonia

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Abstract

Introduction. MRI-guided focused ultrasound (MRgFUS) is approved for management of various movement disorders, primarily essential tremor and Parkinson's disease (PD), with favorable long-term outcomes in numerous patients worldwide. However, few case studies describe the use of this modality for symptomatic treatment of dystonias that, as the third most common movement disorder, may be rather disabling.

Objective: To improve outcomes in patients with cervical dystonia (CD) using MRgFUS.

Materials and methods. We retrospectively analyzed 13 cases of various CD types managed with MRgFUS in single or multiple sessions. The mean age of the patients was 42 [39; 53] years. The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) was used to assess patients' statuses and severity of CD symptoms during therapy and the last available observation period. The targets included the pallidothalamic tract and the thalamic ventral oralis complex nucleus or their combination.

Results. The mean follow-up period was 13.3 ± 3.4 months (July 2021 to April 2023). The mean CD severity sum score (TWSTRS score) was 22 [16; 25] before MRgFUS and 6 [4; 9] in the last observation. Therefore, we report 70.6% [55.6; 76.5] improvement (paired samples t-test $p = 0.0025$).

Conclusion. Available data evidence that MRgFUS is efficient and sufficiently safe for symptomatic treatment in pharmacoresistant CD patients. A number of vital aspects of MRgFUS have to be specified in larger CD cohorts in the long-term follow-up.

Keywords: MRI-guided focused ultrasound; cervical dystonia; thalamic ventral oralis complex nucleus; pallidothalamic tract; ventral interposed nucleus; pallidothalamic tractotomy

Ethics approval. The study was conducted with the informed consent of the patients. The research protocol was approved by the local Ethics Committee of the Research Center of Neurology (protocol No. 1-8/23, January 25, 2023).

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Фокусированный ультразвук под контролем МРТ в лечении цервикальной дистонии

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Аннотация

Введение. Фокусированный ультразвук под контролем МРТ (МР-ФУЗ) одобрен для лечения различных расстройств движений, в первую очередь эссенциального тремора и болезни Паркинсона, причём такие вмешательства, выполненные в мире на многих сотнях пациентов, сопровождаются благоприятными долгосрочными результатами. Однако в доступной литературе описаны лишь единичные случаи использования данной технологии для коррекции симптомов дистоний, которые могут быть весьма инвалидизирующими и по распространённости занимают третье место среди всех клинических форм расстройств движений.

Цель исследования — улучшение результатов лечения пациентов с цервикальной дистонией (ЦД) при помощи технологии МР-ФУЗ.

Материалы и методы. Ретроспективно проанализированы данные 13 пациентов с различными типами ЦД, которым проводилось лечение с помощью МР-ФУЗ поэтапно или одномоментно. Средний возраст пациентов составил 42 [39; 53] года. Состояние пациентов и выраженность симптомов ЦД оценивали по шкале спастической кривошеи Западного Торонто (TWSTRS, оценка тяжести ЦД) во время лечения и в последний доступный период наблюдения. В качестве мишеней использовали паллидоталамический тракт и вентрооральное ядро таламуса или их комбинацию.

Результаты. Средний период клинического наблюдения за пациентами составил 13,3 ± 3,4 мес (с июля 2021 г. по апрель 2023 г.). Средняя сумма баллов по шкале TWSTRS (оценка тяжести ЦД) составила 22 [16; 25] до МР-ФУЗ и 6 [4; 9] — в последний доступный период наблюдения. Таким образом, достигнуто улучшение на 70,6% [55,6; 76,5] (парный критерий Вилкоксона $p = 0,0025$).

Заключение. Имеющиеся данные позволяют говорить, что МР-ФУЗ является эффективным и достаточно безопасным методом коррекции симптомов ЦД, резистентной к фармакологическим методам лечения. Многие важные аспекты применения МР-ФУЗ у пациентов с ЦД ещё предстоит уточнить на более обширных когортах больных в рамках многолетнего катamnестического наблюдения.

Ключевые слова: фокусированный ультразвук под контролем магнитно-резонансной томографии; цервикальная дистония; вентро-оральное ядро таламуса; паллидоталамический тракт; вентральное промежуточное ядро таламуса; паллидоталамическая трактомия

Этическое утверждение. Исследование проводилось при добровольном информированном согласии пациентов. Протокол исследования одобрен локальным этическим комитетом ФГБНУ НЦН (протокол № 1-8/23 от 25.01.2023).

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Introduction

Cervical dystonia (CD) is the most prevalent ($\leq 50\%$) clinical dystonia type. CD is a focal dystonia, with involuntary tonic contractions or intermittent spasms of neck muscles and resulting abnormal neck and head position and/or head tremor [1–5]. The CD prevalence is 1.2–5.7 per 1,000,000 person-years [2], while the CD incidence is 8–12 per 1,000,000 person-years [3], with the manifestation peak falling at the age of 30–50 years [2–4]. The disorder is twice as common in female patients [2]. CD etiology varies. There are congenital (idiopathic) and acquired dystonias [5–7]. Idiopathic CD is shown to be related with *DYT2*, *DYT13*, *DYT23*, *DYT24*, *DYT25*, and other loci mutations [8]. Acquired dystonias develop in patients with the brainstem and basal ganglia lesions of various origin, as a result of long-term use of dopamine receptor antagonists, etc. [4, 8]. Patients with dystonia manifestations often demonstrate functional (psychogenic) disease, which requires special attention and diagnosis experience [9].

CD symptoms typically progress within the first several years up to plateau [4, 5]. Clinically, CD implies the abnormal position of the head (torticollis, torticaput, laterocollis, laterocaput, anterocollis, anterocaput, retrocollis, retrocaput), the neck, and the shoulders with dystonic head tremor aggravated in voluntary movement,

fatigue, and emotional strain. Many patients use sensory tricks, such as touching the chin or cheek, to reduce symptoms. CD is often complicated with depression, anxiety, and phobias and makes patients highly incapable, and limits their daily living and social life [3–5, 10]. While several scales are used to assess CD symptom severity, the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) is the fittest and most widely used [11].

Recently, CD management has transformed dramatically, from exercise therapy, pharmaceutical treatment, and local muscle surgeries through stereotactic ablation and deep brain stimulation (DBS) to innovative non-invasive approaches like MRgFUS [6, 7, 12–17]. Oral agents (clonazepam, anticholinergic agents, myorelaxant agents, etc.) are as a rule ineffective and have significant side effects in therapeutically necessary higher doses [4, 16]. Currently, the gold standard of CD therapy is the use of botulinum toxin type A to treat abnormal movements and to relieve pain [6, 7]. Its disadvantages include the need for repetitive injections every 3–4 months, inadequate effectiveness that depends on CD signs and symptoms, effectiveness decrease, and resistance in some patients [16, 18].

CD surgical treatment dates back to 1641 when the German surgeon named Isaac Minnius sectioned the sternocleidomastoid muscle [10]. Such local interven-

tions had been popular before mid-20th century when the rise of functional stereotactic surgery revolutionized CD neurosurgical treatment and laid the foundation of today practice including DBS and MRgFUS. Soviet and Russian neurosurgeons gained abundant experience in destructive surgery for dystonia [10, 19–21].

In the 1970s, based on W. Hess's experimental results, R. Hassler and G. Dieckmann attempted to consider CD clinical signs and symptoms and to select destruction targets in order to involve the pallidothalamic tract (PTT) in H1 Forel's field (in torticollis) and the thalamic ventral oralis (Vo) complex nucleus (in laterocollis) contralaterally to the head turn side [22, 23]. Following up 112 CD patients post ventro-lateral thalamotomy, E.I. Kandel concluded that the bilateral intervention was more efficient, especially in patients with head hyperkinesias [19]. Follow-up results correspond to the current understanding of CD pathogenesis [14, 24, 25].

Prior to DBS large-scale implementation, destructive surgery was the leading approach in CD symptomatic treatment with effectiveness of 50–70%. Such interventions were performed mostly unilaterally because bilateral destruction was typically (20–70%) complicated by dysarthria, dysphagia, ataxia, and symptomatic parkinsonism [12, 14, 24].

In the late 20th century, DBS became the leading approach in CD neurosurgical treatment [15, 26, 27]. Right and left globus pallidus internus stimulation (GPI-DBS) is the modality commonly used in patients with CD who did not respond to pharmaceutical and botulinum toxin therapies. Improvement after bilateral GPI-DBS may vary from TWSTRS score 27.8% [15] to TWSTRS score 51.4% [27] or 66.6% [28], depending on stimulation parameters, patient cohorts, and observation periods. According to J. Volkman et al., 10% of the patients did not respond to GPI-DBS despite multiply varied stimulation parameters [17].

The clinical implementation of MRgFUS to treat movement disorders revitalized functional brain destruction. Recently, we have accumulated extensive evidence of MRgFUS safety and efficiency in patients with essential tremor and Parkinson's disease (PD) [29–32]. However, by the moment, we have found only single reports on MRgFUS to treat dystonia [13, 33, 34]. We are presenting our own experience of MRgFUS use to manage patients with CD.

Objective. To improve outcomes in patients with CD using MRgFUS.

Materials and methods

We retrospectively analyzed 13 cases of various CD types managed with MRgFUS in single or multiple

sessions. The mean age of the patients was 42 (39; 53) years (Fig. 1). All of them had no family history of dystonia. The disorder manifested as dystonic hand tremor or at early age with subsequent cervical involvement in 2 patients. In other cases, hyperkinesia manifested as isolated CD and was not combined with any other movement disorders.

All the CD patients were refractory to botulinum toxin therapy after several courses. DBS was rejected due to patients' disregard of head mechanical implants (patients' refusal) or lack of access to the medical centers that could adjust stimulation parameters.

TWSTRS was used to assess patients' statuses and severity of CD symptoms during therapy and the last available observation period. The Hospital Anxiety and Depression Scale (HADS) and the Montgomery–Åsberg Depression Rating Scale (MADRS) were used to assess anxiety and depression [11].

MRgFUS CD symptomatic treatment was conducted at V.S. Buzaev Memorial International Medical Center. We used ExAblate Model 4000 (Insightec v.7.0.404, Insightec), with 1024 ultrasound generators, and GE Optima MRI scanner (MR450W, 1.5 T). The standard procedure of preparation for MRgFUS was performed in all the patients.

Targets included PTT and/or Vo (see Table). As there is no unified standard or rationale, targets are selected based on published experience in specific CD cases. Reverse ultrasound exposures allow to model effects in a particular brain area and to select the most efficient target for the patient. The targets were sonicated at least twice at temperature over 55°C. The median MRgFUS time was 117 (79; 139) min; the median sonication number was 12 (11; 14.5). The energy range was 20,096–35,731 J in a temperature range 54–62°C.

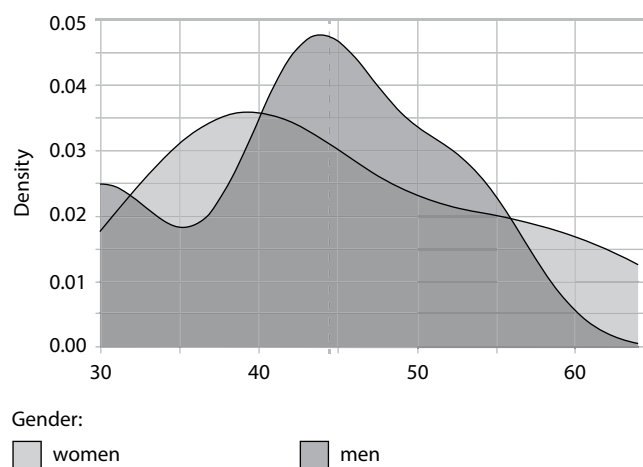


Fig. 1. Age distribution of operated CD patients.

Characteristics of included CD patients

CD clinical signs and symptoms	MP-ΦY3 MRgFUS age	CD onset age	Sex	TWSTRS score – assessed CD severity		Target	
				pretreatment	post treatment	right hemisphere	left hemisphere
Right torticollis, right torticollis, head tremor	42	4	M	16	9		PTT VO
Left torticollis, left laterocollis, head tremor	53	33	M	22	6	PTT VO	
Right torticollis, head tremor	53	43	F	22	4		PTT VO
Right torticollis, head tremor	36	31	F	23	6		PTT VO
Right torticollis, head tremor	39	23	F	4	0		PTT VO
Left torticollis, right laterocollis, orofacial dystonia	39	37	M	27	9	VO	PTT
Left torticollis, left laterocollis, head tremor	42	18	F	17	4	PTT VO	
Right torticollis, left laterocollis, orofacial dystonia	57	26	M	29	15	VO	PTT
Left torticollis, retrocollis	46	33	F	26	10	PTT	VO
Left torticollis, head tremor	30	15	M	9	4	PTT	
Right torticollis, head tremor	57	27	F	13	2		PTT VO
Right laterocollis, head tremor	32	17	F	17	5	VO	PTT
Right laterocollis	47	27	F	25	14		PTT

Note. M, male; F, female.

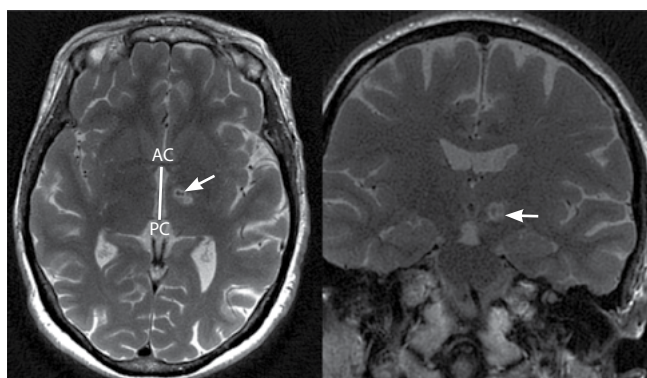


Fig. 2. Axial and coronal MR images in 30 days after right PTT MRgFUS destruction. The arrow indicates the destruction focus.

The MRgFUS procedure included control brain MRI scan (T2-weighted; axial, sagittal, and coronal views; 2-mm thick slices). Intraoperative imaging showed no signs of hemorrhage or non-target heat in any patient. Follow-up brain MRI scans in 2 h and 24 h, and 30 days revealed slight marginal edema (1–3 mm) and necrotic foci at the sites of sonication (Fig. 2).

Results

The mean follow-up period was 13.3 ± 3.4 months (July 2021 to April 2023). The mean CD severity assessment (TWSTRS score) was 22 [16; 25] before MRgFUS and 6 [4; 9] in the last available observation. Therefore, we found 70.6% [55.6; 76.5] improvement (paired samples t-test $p = 0.0025$).

Six patients demonstrated mild side effects including gait disorders and postural unsteadiness for 3 weeks. Two patients had significant logorrhea totally reversed on quetiapine (25 mg/day) within a month. Two female patients noted memory deterioration in 1 month post MRgFUS followed by gradual recovery by the end of the follow-up year 1. Two patients showed altered handwriting with slight micrography and gradual post-operative recovery.

One patient with significant head tremor showed recurrent hyperkinesia in 6 months post MRgFUS. This patient received re-intervention in 9 months post initial procedure, with no recurrent head tremor during next 4 months.

The patients reported evident positive changes in their daily living and their social and professional lives throughout the follow-up period. Three patients got better-paid job positions; one patient changed nighttime IT position for academic lecturing; one female patient was proposed to get married; one patient stopped having the status of disabled person; one patient resumed working as an operating surgeon; two patients resumed their occupations.

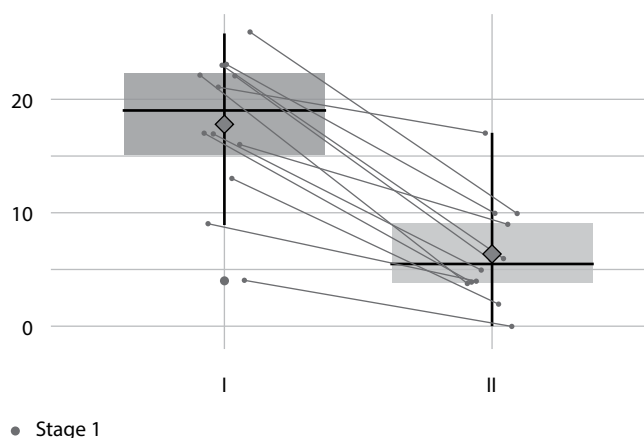


Fig. 3. TWSTRS scores pre (I) and immediately post (II) MRgFUS intervention.

Discussion

Management of CD patients remains a challenge for neurologists [4, 5, 16, 18]. DBS is the best option that can significantly relieve CD symptoms [15, 26], but it is not widely used due to its complexity and low accessibility. MRgFUS can become an alternative, innovative, and non-invasive method of functional neurosurgery in this population though the experience of its use for CD (unlike PD and essential tremor) is especially limited and, according to the guidelines, MRgFUS is no method of choice [13, 33, 34].

In 2021, S. Horisawa et al. published an open-label pilot study and showed that Vo MRgFUS significantly relieved focal hand dystonia in 10 patients, with mild dysarthria in 1 patient as the only adverse event in 12 months [13]. R. Jamora et al. demonstrated general improvement in 3 patients with X-linked dystonia-parkinsonism (XDP) post MRgFUS Vo-thalamotomy [34]. The XDP-MDSP scores improved by 36.2% in 6 months and by 30.1% in 12 months. However, central pain syndrome manifested in 2 patients in 2–7 months post treatment.

We have described our own, first experience in Russia of the MRgFUS use for CD (in 13 patients with follow-up period over 1 year and TWSTRS improvement by 70.6%). Due to recurrent tremor, one patient received re-intervention in 9 months after initial procedure. Complications were relatively mild and resolved by the end of follow-up year 1. We selected PTT and/or Vo as targets, basing on published intervention outcomes in relevant patient categories [13, 14, 33, 34]. So, PTT destruction relieves CD symptoms due to disruption of cortico-basal and thalamo-cortical pathways and modulation of thalamic efferent stimuli while Vo interventions may be useful in patients with laterocollis [25, 35].

Available data allow us to consider MRgFUS as an efficient method to treat symptoms of pharmacoresistant CD. A number of vital aspects of MRgFUS have to be specified in larger CD cohorts in long-term follow-up. This method may be considered as advanced in manage-

ment of patients with other dystonias, which has to be proven in special studies including multicenter trials. We may expect that, introduced into clinical practice more widely, this mini-invasive method will be gradually used in patients with movement disorders more extensively.

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