Research Article
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Stereotactic Radiosurgery in the Complex Treatment of Patients with Epilepsy Associated with Various Structural Brain Lesions

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BACKGROUND Structural damage to the brain substance in adults is one of the most common causes of epilepsy. Currently, such patients are prescribed drug therapy and/or surgery. With this approach, epileptic symptoms can persist in a significant proportion of patients (up to 30%, depending on the disease).

AIM OF STUDY To clarify the efficacy of stereotactic radiosurgery (STS) as part of the complex treatment of patients suffering from pharmacoresistant symptomatic epilepsy with hippocampal sclerosis, vascular malformations, and some benign tumors of the brain and its membranes.

MATERIAL AND METHODS

Examination and radiosurgical treatment were carried out in 45 patients with various brain diseases accompanied by symptomatic epilepsy, provided that the previous conservative or surgical treatment was insufficiently effective. During the observation period, the frequency of seizures was assessed and the presence and nature of postoperative complications were recorded.

RESULTS With a median follow-up of 30 months, good outcomes (class I–II according to J. Engel's scale) were observed in 5 out of 8 patients with hippocampal sclerosis who underwent STS after amygdaloghippocamplobectomy; seizure frequency decreased in all patients. Complications of STS were noted in 2 patients and had a transient nature. In the group of patients with meningiomas, in 4 out of 8 patients, seizures completely stopped, in 3 patients the frequency of seizures decreased by more than 90%, in another 1 the frequency of seizures decreased by 60%. There were no complications of STS during the observation period. In intracerebral tumors (diffuse astrocytoma), Engel Ia outcome was observed in both patients. In the group of patients with cavernous angiomas, there were good outcomes (class I–II according to J. Engel's scale) in 17 patients (85%). Deterioration (Engel IVc outcome) was observed in 1 patient (5%), 2 patients (10%) had complications of STS. In the group of patients with arteriovenous malformations, good outcomes (classes I–II according to J. Engel's scale) were found in all 7 patients. The complication after STS was revealed in 1 patient.

CONCLUSION The presented results confirm the high efficiency and low risk of side effects when using stereotactic radiosurgery in the complex treatment of patients with epilepsy associated with common structural brain lesions.

Keywords: stereotactic radiosurgery, epilepsy, hippocampal sclerosis, meningioma, diffuse astrocytoma, cavernous angioma, arteriovenous malformation

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ACT - anticonvulsant therapy
AHE - amygdaloghippocampectomy
AVM - arteriovenous malformations
CA - cavernous angiomas
CAG - cerebral angiography
CT - computed tomography
EEG – electroencephalography
LGGDT – low-grade glial diffuse tumors
MRI - magnetic resonance imaging
PD - prescribed dose
SRS - stereotactic radiosurgery

INTRODUCTION

One of the main etiological factors for the onset of epilepsy in adults is structural damage to the brain substance [1]. Arteriovenous malformations (AVM), cavernous angiomas (CA), intra- and extracerebral tumors, phakomatosis (tuberous sclerosis, neurofibromatosis, Sturge-Weber syndrome, etc.) should be noted among the various brain diseases that most often lead to the onset of epilepsy. For the treatment of patients with these diseases, the method of stereotactic radiosurgery (SRS) is increasingly used, which allows local, mainly single, high-dose irradiation of the pathological focus [2].

In 1992 J.C. Sutcliffe et al. found a decrease in the number of seizures after SRS in patients with AVM without any changes in the irradiated focus on computed tomography (CT) [3]. Over the past 30 years, the number of patients who underwent radiosurgery has increased significantly. The mechanisms of the effect of ionizing radiation on the pathological focus have been studied in detail: apoptosis of tumor cells, obliteration of AVM vessels, proliferation of fibroblasts in the walls of the coronary artery, etc. [4–8]. However, the pathophysiological mechanisms of the effect of SRS on epileptogenesis in many cases remain unclear [2, 9, 10].

For a significant proportion of patients with epilepsy associated with structural brain lesions, epileptic seizures are the main and sometimes the only clinical symptom [6, 10-14]. In the Russian-language literature, there are no works evaluating the antiepileptic efficacy of SRS in the complex treatment of such patients.

Aim of study: to clarify the effectiveness of stereotactic radiosurgery as part of the complex treatment of patients suffering from pharmacoresistant symptomatic epilepsy with hippocampal sclerosis, cerebral vascular malformations, some benign tumors of the brain and its membranes.

Objectives:

1. To reveal the peculiarities of diagnosis and clinical course of the disease in groups of patients with brain diseases of various etiology, accompanied by symptomatic epilepsy.
2. Clarify the specifics of planning SRS in these groups of patients.
3. Evaluate the results of the SRS carried out.
4. Determine the frequency and nature of postoperative complications.

MATERIAL AND METHODS

In the period from 12.04.2016 to 31.12.2019, 45 patients with structural lesions of the brain substance suffering from epilepsy were examined and treated according to the ILAE criteria [15]. The characteristics of patient groups are presented in Table 1.

Table 1

Characteristics of groups

Group	Diagnosis	Number of patients	Age, years	Volume of target, sm^3	PD, Gy	Isodose, %
1	Hippocampal sclerosis	8	M=35,5±10,3	M=3,44±0,97	Me=20,5 (20;22,5)	50–65
2	Meningioma	8	M=54,1±16,7	Me=2,59 (1,71;7,29)	Me=14 (13;14)*	50–70
3	Intracerebral tumors	2	37 и 50	0,5 и 15,75	15 и 16	50
4	CA	20	M=41,8±13,9	M=0,97±0,81	Me=20 (18;22)	50–70
5	AVM	7	M=32,1±11,4	Me=4,83 (1,7;4,36)	M=19,75±2,3	50–55

Notes: * — the prescribed dose was 6.5 Gy for the patient with the stereotactic radiosurgery. ABM — arteriovenous malformations; KA — cavernous angiomas; ПД — prescribed dose in Grays (Gy)

The study group did not include patients with primary and secondary malignant brain tumors, since the short possible follow-up period and the heterogeneity of the treatment (radiation therapy, chemotherapy, corticosteroids) did not allow to unambiguously determine the antiepileptic effect of SRS.

All patients underwent comprehensive examination, consisting of neurological examination, clinical analysis of the semiotics of seizures, and magnetic resonance imaging (MRI) on the device with a magnetic induction of 3T. To clarify the location of speech zones, two patients underwent functional MRI of the brain. Three patients underwent electroencephalography (EEG), combined with MRI of the brain in order to verify the location of the epileptogenic focus. Three patients with a doubtful clinical picture underwent continued video-EEG monitoring with registration of ictal events, which confirmed the onset zone of an attack of the corresponding location. For patients who had previously undergone open neurosurgical surgery, the data of histopathological examination of the removed tissue were available.

All patients with hippocampal sclerosis have previously undergone amygdaloghippocampectomy (AHE). In 4 patients, predominantly focal-onset seizures accompanied by a change in consciousness were observed; in 4 patients, predominantly non-motor generalized seizures were observed.

Among patients with meningiomas, 6 patients had previously undergone microsurgical removal of the tumor. In 4 of them, epileptic seizures were observed before surgery, in 2 patients the first seizure developed within 6 and 12 months after surgical treatment.

Histological diagnosis in all cases: meningotheliomatous meningioma. In 6 patients, the tumor was located in the frontal region, in 1 - in the temporal region, and in 1 patient - in the parietal region. In 4 patients, only focal seizures with a motor onset were observed, in the remaining 4 patients, both focal seizures and generalized tonic-clonic seizures were noted.

All patients with intracerebral tumors underwent microsurgical removal of the tumor; no additional radiation or chemotherapeutic treatment was performed. After the operation, epileptic seizures persisted, mainly of a focal nature. Histological diagnosis: diffuse astrocytoma.

In the group of patients with cavernous angiomas, in 5 people (25%), a focus of pathological vascular tissue was detected in the frontal lobe, in 8 (40%) - in the temporal lobe, in 3 (15%) - in the parietal lobe, in 2 (10%) - in the occipital lobe, 1 patient (5%) had CA of thalamic location, and 1 (5%) - CA of multiple location, some of which were previously removed due to the formation of intracerebral hemorrhages with focal neurological symptoms. According to the MRI of the brain, 18 patients (90%) had previously suffered a rupture of the coronary artery. In 4 patients (20%) only focal seizures were noted, in 12 (60%) - only generalized seizures, in 4 (20%) - a combination of focal and generalized seizures.

In the group of patients with AVM, the focus was in the frontal lobe in 1 patient, in the temporal lobe in 4 patients, in the parietal lobe in 1 patient and in the occipital lobe in 1 patient. Three patients had AVM rupture. Four patients had only generalized seizures, the other 3 patients had a combination of focal and generalized seizures.

A total of 42 patients (93%) were registered with an epileptologist and received anticonvulsant therapy (ACT); only patients with hippocampal sclerosis met the criteria for drug resistance. The reasons for refusing ACT were renal failure in 1 patient (2%) and drug intolerance - in 2 (4%).

The radiosurgical operation was started with the installation of a stereotactic frame according to the generally accepted technique. In cases where standard fixation points were unavailable due to a previous craniotomy, the stereotactic frame was attached with a rotation about the Z axis by 30–45 °. The second stage was MRI of the brain in T1 and T2 modes for patients with CA, T1 and 3D-TOF and selective digital subtraction cerebral angiography (CAG) for patients with AVM; T1 and Flair for patients with hippocampal sclerosis; T1 with intravenous contrast and Flair for patients with intra- and extracerebral tumors. Then, the DICOM images were sent to the planning station with the Leksell GammaPlan 10.2 software, where the operating team, consisting of a neurosurgeon, medical physicist and radiologist, created the contours of the pathological focus and, if necessary, functionally significant structures of the brain (part of the visual analyzer, brain stem, Broca area).

For patients with sclerosis of the hippocampus, the target was the residual fragments of the amygdala, the anterior 2/3 of the hippocampus, and the underlying parahippocampal gyrus. For AVMs, the target volume was determined based on the synthesis of MRI and CAG data in the arterial phase, before the appearance of distinct contrasting of the efferent vessels. With CA, the contour of the target was marked on T1-weighted images so that it was within the hypointense zone on T2-weighted images (zone of perifocal hemosiderosis). The formation of the contour of meningiomas was performed on the basis of pathological accumulation of a contrast agent by the tumor without the capture of "dural tails". Intracerebral tumors were contoured along the edge of the hyperintense zone based on the data of positron emission tomography combined with CT of the brain with 11C-methionine.

The volume of the focus formed on the basis of the contour was then sequentially filled with isocenters in such a way that the planned target volume (Planned Target Volume, PTV) most closely matched the volume and shape of the focus. The minimum coverage and selectivity indicators were set by us as 95% and 70%, respectively. The regional prescribed dose is assigned on the basis of international clinical guidelines for each specific disease [2, 8, 9, 16-18]. For 1 patient with a meningioma in the left temporal region, SRS was used in hypofractionation mode (3 fractions of 6.5 Gy) due to a significant tumor volume and the presence of contraindications to open neurosurgical surgery (taking anticoagulants).

After SRS, patients underwent MRI every 6 months after surgery, the number of epileptic seizures was counted and the presence of SRS complications was assessed over the entire follow-up period [19]. The median follow-up was 30 months (T0.25 = 15.9, T0.75 = 49.9).

Statistical data are tabulated and processed using Statistica 10 software (StatSoft, Inc). The Lilliefors and Shapiro-Wilk tests were used to assess the nature of the distribution in the aggregate based on sample data. Numerical data are presented as mean and standard deviation (M ± SD) with a normal distribution or median (ME) of the 25th and 75th percentiles for distributions other than normal.

RESULTS

STEREOTACTIC RADIOSURGERY FOR HIPPOCAMPUS SCLEROSIS

All patients managed to achieve improvement in the form of a decrease in the frequency of attacks and / or changes in the structure of the attack. Class I outcome according to J. Engel scale was noted in 1 patient. In 4 patients, the outcomes corresponded to class II: IIA - 1 patient, IIB - 2 patients, IIC - 1 patient (Fig.1A).

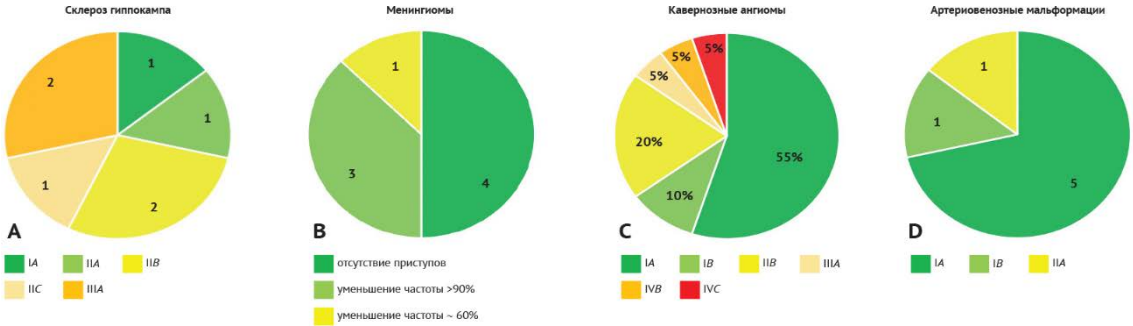

Fig. 1. Results of treatment of patients in groups 1, 2, 4, 5 (A, B, C, D, respectively)

The outcome of class IIIA was observed in 2 patients, one patient subsequently underwent implantation of a vagus stimulator, after reaching the recommended stimulation parameters, full control over the seizures was achieved; IVA outcome was observed in 1 patient. Doses and frequency of administration of antiepileptic drugs remained unchanged during the observation period.

Complications of SRS were observed in 2 patients. After 6 months, radiation leukoencephalopathy of the temporal lobe developed in 1 patient, accompanied by a transient increase in the frequency of seizures with focal onset; radionecrosis in the irradiated area without any new neurological symptoms and with positive dynamics upon further observation developed in another patient 6 months later.

STEREOTACTIC RADIOSURGERY FOR MENINGIOMAS

After SRS, 7 patients achieved a good clinical effect (in 4 patients complete cessation of seizures, in 3 patients their frequency decreased by more than 90%), in 1 patient the seizure frequency decreased by 60%. Antiepileptic drugs were discontinued in 3 patients (Fig. 1B). The volume of the irradiated tumor 1 year later decreased in 2 patients, did not change in 5 patients, and increased in 1 patient, which required repeated SRS. There was 1 death due to reasons unrelated to intracranial pathology. There were no complications of SRS during the follow-up period.

STEREOTACTIC RADIOSURGERY FOR INTRACEREBRAL TUMORS

For both patients, the IA result was obtained, the dosage of antiepileptic drugs was reduced. The postoperative period was uneventful.

STEREOTACTIC RADIOSURGERY FOR CAVERNOUS ANGIOMAS

Good outcomes (class I – II according to J. Engel scale) were observed in 17 patients (85%): 11 (55%) - IA, 2 (10%) - IB, 4 (20%) - IIB. Outcome IIIA was observed in 1 (5%) patient, IVB - also in 1 (5%). Deterioration (IVC outcome) was detected in 1 (5%) patient (Fig. 1C). Antiepileptic drugs were discontinued in 7 patients (35%), their dose was reduced in 3 (15%). In 1 (5%) patient in the postoperative period, a repeated rupture of the cavernous angioma with a temporary increase in the frequency of attacks was revealed; asymptomatic radiation necrosis developed in 2 (10%) patients (outcomes IA and IIIA).

STEREOTACTIC RADIOSURGERY FOR ARTERIOVENOUS MALFORMATIONS

After SRS, 5 patients had outcome IA, 1 patient - 1B, and 1 patient - IIA (Fig.1D). Volumetric analysis was available for 5 patients: in all 5 cases, the AVM volume decreased 1 year after SRS. Obliteration of AVM, according to MRI, was noted in 2 patients. Asymptomatic radiation necrosis developed in one patient.

DICUSSION

Currently, the mechanisms of epileptogenesis in hippocampal sclerosis have been studied to the greatest extent [20–22]. Numerous studies confirm the highest efficiency and safety of microsurgical resection of the temporal lobe in comparison with other methods of treatment [23–26]. However, in case of insufficient efficacy of the performed operation, repeated surgical treatment is most often assigned. The main reasons for the persistence of seizures in the postoperative period with structural lesions of the temporal lobe are listed in the work of C.M. Reed et al .:

1) limited and insufficient primary resection;

2) tumor recurrence;

3) the presence of epileptic activity from the opposite side [27].

According to the review by R. Yardi, the absence of seizures after reoperation is observed in 50% of patients [28]. In connection with the development of minimally invasive neurosurgery in world practice, methods such as stimulation of the vagus nerve (vagal nerve stimulation, VNS), stimulation of deep brain structures (deep brain stimulation, DBS), laser ablation of the focus (laser interstitial thermal therapy, LITT) are also considered, and finally SRS. These methods can be used if the patient refuses to undergo open neurosurgical surgery or if there are contraindications to it.

In the literature, more attention is paid to the use of SRS as an independent method for the treatment of drug-resistant epilepsy in hippocampal sclerosis: only one work has been published describing the combination of microsurgical resection of the temporal lobe and radiosurgical treatment. So, E.M. Lee et al. reported the result of the level I – II class according to the J. Engel scale for 7 of 12 patients who underwent SRS after AHE [29]. For patients with a resistant course of the disease, this approach is justified not only theoretically: a lower risk of radiation toxicity is assumed due to the smaller volume of irradiated tissues after resection of the temporal lobe, which is confirmed by our data.

It should be noted that the J. Engel scale, traditionally used in neurosurgery, is not quite suitable for assessing the effect of SRS. In particular, classes IC, IIIB are inapplicable, suggesting the simultaneous removal of an epileptogenic focus without taking into account the latency of SRS action and the possibility of radiation toxicity. The maximum anticonvulsant effect in SRS is achieved on average after 11.5 months,

and at the same time, an increase in the frequency of seizures associated with the effect of neuromodulation (usually 9–12 months after SRS) or the development of radiation complications is possible [9].

Epileptic seizures are common in patients with intracranial meningiomas (27–67%) and are the main symptom at the onset of the disease [30]. Open neurosurgical surgery leads to the disappearance of seizures in 62.7% of patients; however, seizures can develop in the postoperative period even in those patients who have not previously suffered from epilepsy (up to 20%) [31]. The number of publications describing the dynamics of epilepsy after radiosurgical treatment of patients with meningiomas is small. Di Franco et al. reported that according to the results of radiosurgical treatment of 52 patients, of whom 24 had previously undergone open surgery, seizure control was obtained in 17% of patients, in 33% of patients the frequency of seizures remained unchanged, and in 33% worsening was observed [32]. In a study by El-Khatib et al. 4 out of 8 patients showed a decrease in the frequency of seizures after SRS [33]. We have obtained a good clinical effect both for patients with residual epilepsy after tumor resection and for patients with epilepsy resulting from surgical treatment.

Among benign intracerebral tumors for diffuse low-grade glial tumors (DLGGT), epileptic seizures are the most common symptom, detected in more than 90% of patients. The risk of developing epilepsy is higher in patients with oligodendroglial tumors and tumors of mixed structure than in patients with astrocytomas [34, 35]. According to the literature, the methods of radiation therapy (up to 75%), as well as surgical resection of the tumor (36–100%) show a high efficiency of control of seizures in DLGGT [10]. Separate studies have been published that assess the results of radiosurgical treatment of both primary diagnosed DLGGT and tumor recurrence after surgical treatment, radiation therapy, or combined treatment, but the role of SRS in the treatment of epilepsy in this type of tumor has not been unambiguously determined [36–39]. Despite the fact that in the present study, seizure control was achieved in all patients with DLGGT, a small number of patients does not make it possible to reliably judge the antiepileptic effect of SRS.

Patients with epilepsy account for 25–40% among patients with AVM and 30–70% among patients with CA [40–42]. Despite the satisfactory effect of anticonvulsants for most patients with AVM and CA, the need for their treatment in many cases is determined not only by the presence of epilepsy, but also by the risk of rupture of the pathological focus with the formation of intracranial hemorrhage [43–45]. Currently, there are no randomized studies in the literature evaluating the effectiveness of a combined approach to the treatment of epilepsy in cerebral vascular malformations in comparison with monotherapy with anticonvulsants [46]. Unlike AVMs, for which the use of SRS leads to obliteration of the pathological vascular network and the elimination of the risk of hemorrhage, the effect of SRS on the probability of coronary artery rupture is not so unambiguous. In the literature, conflicting data are described: some groups of researchers note a decrease in the risk of hemorrhage only for patients who underwent SRS after coronary artery rupture, others do not find a similar effect [18, 45, 47–49]. The antiepileptic effect of SRS, according to the literature data, was found in 73–84.9% of patients for CA and in 55–89% of patients for AVM, however, complete cessation of seizures occurs less frequently [40, 46, 48, 50–53].

The results of this study confirm the high efficacy of SRS and the low risk of complications in patients with epilepsy associated with CA and AVM, however, to assess the delayed effects of radiation toxicity and their impact on the quality of life, a much longer follow-up period (at least 10 years) is required.

CONCLUSION

The presented results confirm the high efficiency and low risk of side effects when using stereotactic radiosurgery in the complex treatment of patients with epilepsy associated with many common structural brain lesions. The use of the stereotactic radiosurgery method is possible against the background of insufficient effectiveness of the conservative treatment, for patients after open neurosurgical operations, as well as in cases where the removal of an epileptogenic focus is associated with an excessive risk for the patient.

FINDINGS

1. Epilepsy in arteriovenous malformation, cavernous angioma and hippocampal sclerosis is more often manifested by generalized seizures and a combination of focal and generalized seizures; for intra- and extracerebral tumors, focal seizures are more characteristic.

2. In the diagnosis of patients with sclerosis of the hippocampus, additional studies are required to visualize postoperative changes - magnetic resonance imaging in T2 and Flair mode with thin slices; For individual patients with hippocampal sclerosis, clinically significant information was obtained thanks to

magnetic resonance imaging with synchronous electroencephalography, as well as 24-hour video-EEG monitoring.

3. Peculiarities of planning radiosurgical treatment, taking into account the presence of epilepsy, are characteristic only for patients with cavernous angioma - inclusion of the zone of perifocal hemosiderosis and sclerosis of the hippocampus in the area of the prescribed dose; structures.

4. Radiosurgical treatment of patients with structural epilepsy associated with arteriovenous malformations, cavernous angiomas, meningiomas, intracerebral tumors and hippocampal sclerosis can significantly reduce the frequency of seizures or their complete cessation in most patients with insufficient effectiveness of previously received conservative treatment or surgical removal of the pathological focus.

5. Side effects of radiosurgical treatment are rare and most patients are asymptomatic.

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