



CLINICAL AND DIAGNOSTIC FEATURES AND EFFECTIVENESS OF SURGICAL TREATMENT OF MESIAL TEMPORAL LOBE EPILEPSY

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ABSTRACT

Despite certain successes in the treatment of epilepsy, primarily associated with the active development of pharmacology, in 30% of cases its resistant course is noted, especially focal forms of temporal epilepsy. One of the main causes is mesial temporal sclerosis (MTS), considered an absolute epileptogenic substrate, not amenable to conservative treatment in 90-92% of cases. Surgical treatment seems to be the only method that helps improve the quality of life of such patients. However, the percentage of surgical care for epilepsy remains low. Structured information on clinical manifestations, diagnostic methods, approaches to surgical treatment and its outcomes should contribute to understanding the problem among specialists. Data on the effectiveness of operations in patients with drug-resistant epilepsy can help in timely provision of high-tech care to patients with mesial temporal epilepsy.

INTRODUCTION

Epilepsy is a serious medical and social problem worldwide. About 70 million people suffer from this disease regardless of gender, race, age or geographic boundaries [1]. In Europe, about 6 million people suffer from epilepsy, in Russia there are up to 500,000 registered cases [2]. Diagnosis and treatment of this disease are resource-intensive, which may be the reason for the significant spread of data between the epidemiological indicators of the regions [1]. Patients who continue to have epileptic seizures despite drug therapy suffer from cognitive and mental disorders, and also have a high risk of injury and sudden death (SUDEP – sudden unexpected death). The most common form of epilepsy is temporal, accounting for 60–70% of focal epilepsies [3]. There are two main forms of temporal epilepsy: mesial (syn. limbic, paleocortical) and lateral (syn. neocortical). This division is not accidental: despite the anatomical affiliation with the temporal lobe, the lateral and mediobasal sections have fundamental differences functionally and morphologically. A third of patients with temporal epilepsy do not have a satisfactory response to drug therapy [4]. Mesial temporal epilepsy (MTE), associated with structural changes in the hippocampal amygdaloid complex, occurs in 60–65% of patients with drug-resistant temporal epilepsy. The pathomorphological substrate of MVE is usually hippocampal sclerosis. The second most common is amygdala damage, and the third is the uncus [5]. In the presence of such epileptogenic anatomical lesions, drug resistance approaches 90–92% [4]. Back in 2003, the



American Academy of Neurology published guidelines for the management of patients with drug-resistant temporal lobe epilepsy, which indicated that if two antiepileptic drugs (AEDs) in adequate therapeutic doses are ineffective, surgical treatment as early as possible is recommended. In 2012, based on a multicenter randomized trial (J. Engel et al.) these recommendations were confirmed. However, statistical data still show a rather low percentage of surgical care for epilepsy even in developed countries [6]. Nevertheless, the most complete possible awareness of doctors about the effectiveness of surgical treatment of patients with drug-resistant epilepsy can help to provide timely high-tech care to this category of patients. Anatomical – histological sections of the temporal lobe. Due to the complex structural and functional organization of the temporal lobe, damage to individual anatomical areas is accompanied by various clinical manifestations.

Thus, the mediobasal parts of the temporal lobes are part of the limbic system of the brain. They include morphological substrates of memory (hippocampus, dentate gyrus) and mental functions (amygdala), as well as structures of the olfactory cortex (uncus, insula) and the pathways of the visual analyzer [7]. Close interconnection of the limbic system with the structures of the diencephalon leads to pronounced vegetative manifestations when it is irritated (cingulate gyrus, parahippocampal gyrus, hippocampus, dentate gyrus). The internal part of the temporal lobe, primarily the hippocampus, in contrast to the external, has a different histological structure. It includes the old (paleocortex) and ancient cortex (archicortex), which have a three-layer cellular architecture. The cells are located in the form of layers of polymorphic cells, pyramidal neurons and a molecular layer. The border between the outer and inner parts of the temporal lobe is the parahippocampal gyrus, which has a transitional structure [8]. The hippocampus is divided into 4 segments by cellular structure: CA1–CA4. Segmental differences consist of the number and size of pyramidal cells. Fields CA1 and CA3 are the main segments of the hippocampus. In fields CA1 and CA2, 2 layers of small pyramidal cells are closely located, continuing into a layer with large, relatively sparsely located cells of segment CA3, the axons of which provide collaterals Schaffer. Collaterals, in turn, contact the pyramidal cells of the CA1 segment, creating the main association pathway. The CA4 segment consists of small pyramidal cells and is surrounded by the gray matter of the dentate gyrus. A granular layer of cells passes under the hilus of the dentate gyrus of the hippocampus. Below is the molecular layer of the hippocampus [9]. In MIS, selective loss and degeneration of pyramidal cells in different segments of the hippocampus is observed; in addition, glial changes are detected. It should be noted that the term "hippocampal sclerosis" implies the presence of pronounced gliosis in its tissue. In some cases, the resulting reactive gliosis can be accompanied by characteristic electrophysiological changes, but due to insufficient expression of tissue restructuring in the hippocampal segments, such changes are not considered mesial sclerosis [10]. The International League Against Epilepticism (ILAE) proposed to classify MBC based on the histological picture. The main advantage of this classification is its universality and ease of use. Standard and accessible methods of staining brain tissue are used. This classification method allows us to distinguish between a typical histological picture (MBC type 1) and an atypical one (MBC types 2, 3). The advantage of this system is the universal possibility to compare the results of different clinics and to correlate them with neuroimaging data [11]. Type 1 is the most



common (60–80% of cases). It is characterized by the loss of more than 80% of pyramidal cells in the CA1 field of the hippocampus, combined with lesser cell loss and gliosis in the remaining segments. Total sclerosis type 1 also includes destruction of the dentate gyrus and more extensive damage to segments other than CA1. Type 2 is characterized by neuronal degeneration and gliosis predominantly in the CA1 field. Type 3 indicates a pathological process in the CA4 segment. The term " gliosis " in this classification is used for small glial changes, most often in the subgranular layer. diagnostics of mesial and jugular sclerosis. Clinical semiotics of epileptic seizures provides important information about the possible localization and lateralization of the epileptic focus. According to the 2017 ILAE classification of epileptic seizure types [12], MVE can manifest itself in various types of seizures: focal with preserved awareness (consciousness), focal with impaired awareness, and focal with transition to bilateral tonic-clonic seizures. In terms of kinematics, seizures most often occur in the form of focal motor seizures with impaired awareness and automatisms (oralimentary, gestural or ambulatory) or focal non-motor seizures with impaired awareness and cessation of action. Sometimes focal sensory disturbances occur in the form of vegetative-visceral abdominal auras, less often olfactory auras (about 1% of all auras) [13], which can precede the seizure or occur in isolation. Patients often suffer from focal motor seizures evolving into bilateral tonic-clonic seizures. Progress in neuroimaging technologies has a significant impact on expanding the possibilities of diagnostic search for etiologic factors of epilepsy, as well as in preoperative preparation and evaluation of the results of surgical treatment of all types of epilepsy [14]. Videoelectroencephalographic monitoring (VEM) and high-resolution magnetic resonance imaging (MRI) are indispensable diagnostic tools for identifying and localizing pathological foci. VEM is highly informative and is currently considered the standard of preoperative examination.

The purpose of VEM in diagnosing MWS is both recording epileptiform patterns and excluding pathologies disguised as epilepsy. From 4 to 10% of patients examined before surgery have comorbid psychogenic seizures, which may progress after surgery [15]. The method also helps to confirm existing diagnostic data and identify other possible epileptogenic foci. Neurophysiological patterns recorded by an electroencephalograph allow localizing the pathological source and indicate the nature of epileptiform activity and its representation. During long-term patient monitoring, the main array of data obtained is the recording of interictal activity. However, the "gold standard" is the recorded ictal activity during seizures habitual for the patient in order to identify the zone of initiation of the paroxysm [15]. For this purpose, a daily or multi-day VEM can be used, during which it is envisaged to cancel or reduce existing drug therapy to increase the likelihood of an attack occurring during the study, and functional provocative tests are also carried out. Classical MRI with a targeted study of the structures of the temporal lobes when mesial temporal sclerosis demonstrates a decrease in the volume of the hippocampus. This zone has a hyperintense signal in the T2 mode. An increase in signal intensity may indicate an increased content of water molecules in glial tissue [16]. Often, MRI shows atrophy of other parts of the limbic system associated with hippocampal sclerosis. It should be noted that routine MRI is often insensitive to hypersclerotic changes in the hippocampus. First of all, this is due to the rather wide slice step, which is more than 5 mm in survey studies [17]. In this regard, optimized



high-resolution MRI is used to visualize hippocampal sclerosis . The minimum slice thickness according to special epiprotocols, which is 0.6–2 mm, in a large percentage of cases allows obtaining sufficient information for visualizing the SWS. Nevertheless, about 30% of drug - resistant epilepsies remain MR-negative [18]. Identification of pathological lesions, especially focal cortical dysplasia (FCD) and hippocampal sclerosis , can be significantly improved using the latest high-field MRI with a magnetic field strength of 7 Tesla. However, this equipment has not yet been introduced into clinical practice, so protocols, modes and analysis capabilities are currently being improved based on existing MRI scanners with a magnetic field strength of 1.5–3 Tesla [18]. Data obtained in scientific studies of patients with MIS using high-field MRI with a power of 7 Tesla have a strong correlation with the results of histological analysis. The sensitivity and specificity values of the detected changes reached 100% [19]. FLAIR (Fluid attenuation inversion recovery) and GRE (gradient-recalled echo) on a high-field tomograph allow us to identify foci of FCD that are not detected at normal powers in one third of cases, but small foci of gliosis still remain undetected. Quite often, positron emission computed tomography (PET/CT) is used to diagnose MWS. In the case of the presence of an epileptogenic zone, according to PET with 18F-FDG (fluorodeoxyglucose), hypometabolism is detected in this area. It is noteworthy that not only the temporal lobe area is involved in this process, but also that hypometabolism often spreads to the insula, frontal lobe, perisylvian region and thalamus. Hypometabolism is more pronounced in right-sided MWS than in left-sided process. Contralateral hypermetabolism, which can be considered as a compensatory mechanism. Moreover, it is more often detected in patients with left-sided MBC and in women. Based on the available data, it can be concluded that MBC is not only a focal lesion, but also a widely integrated, structurally altered brain tissue affecting other areas of the brain [20]. In cases where there is insufficient data on the localization of the lesion, or when the results of non -invasive diagnostic methods, resort to invasive electroencephalography (EEG). Invasive EEG can be performed using subdural electrodes (plates, grids) or using deep electrodes (stereo-EEG). Both options are effective and give good results. VEM with invasive electrodes allows localizing a clear focus of epileptiform activity in a certain area of the brain. In the work of M. Hupalo et al . (2017) conducted an analysis of studies of 62 patients with drug-resistant epilepsy. Among them, VEM, conducted with scalp electrodes, made it possible to determine the focus of pathological activity in 69% of cases. The remaining patients did not have data on the clear localization of the epileptogenic zone, and subsequently 53% of these patients underwent diagnostics using deep electrodes, 31% of patients - with the help of subdural and the remaining 16% - with the help of sphenoid electrodes.

As a result, epileptiform activity was "localized" in all patients [21]. During surgery for hippocampal sclerosis, invasive EEG is also used with the help of electrode plates electrocorticography, ECoG, when the bioelectrical activity of the brain is recorded directly from the cerebral cortex. Thanks to such methods, the most accurate localization of epileptiform activity is revealed to indicate the boundaries of resection. This allows for maximum excision of the pathological substrate while preserving healthy brain tissue. In most cases, at the final stage of resection of sclerotic structures, a decrease in the representation and intensity of epileptiform activity is observed on ECoG [22]. In our country, intraoperative



ECoG has been actively used in the last decade, which significantly improves the outcomes of surgical treatment of mesial temporal epilepsy [23]. In some cases of temporal epilepsy, the source of epileptic activity is not one focus. Thus, the primary focus can be located in the lateral cortex, and changes in the medio-basal regions are formed secondarily relative to it. This pathology occurs with great variability in 9-30% of patients with temporal epilepsy [24]. In the progressive uncontrolled course of monotemporal epilepsy, an independent epileptic focus ("mirror focus") is formed in 17-30% of patients contralateral hemisphere [25]. In this case, we are faced with the problem of bitemporal epilepsy, which often requires the use of invasive diagnostic methods, as well as several other approaches to surgical treatment. In particular, they resort to implantation of a vagus nerve stimulator or a deep structure stimulator.

The most common types of surgical interventions for epilepsy are open resection operations [26]. Among them, anterior medial temporal lobectomy with amygdalohippocampectomy and selective amygdalohippocampectomy are distinguished, which are performed through transsylvian transcortical or infratemporal approaches. The volume of resection is determined by the presence of important functional zones in the area of intervention [27]. New surgical techniques include stereotactic radiosurgery (SRS), MRI-guided laser interstitial thermal therapy (MgLiTT), and stereo-EEG-guided radiofrequency thermocoagulation (SEEG-guided RFTC) [26]. Unfortunately, in some cases of drug-resistant epilepsy, surgical intervention is impossible. Limitations may be associated with the presence of multiple epileptogenic foci, the impossibility of localizing the focus, or the location of the pathological substrate, which is dangerous for any surgical intervention (primarily due to the proximity of functionally significant zones) [28]. For such patients, neurostimulation techniques are used, including vagal stimulation (Vagus nerve stimulation (VNS), deep brain stimulation (DBS), flexible sensory stimulation (Responsive neurostimulation - RNS). Compared to resection and thermocoagulation techniques, neurostimulation is considered a palliative procedure. However, it helps to reduce the number of seizures, and in exceptional cases, even eliminates them [28]. However, there is no direct comparison of neurostimulation techniques with each other due to methodological difficulties. outcomes of surgical interventions. Currently, most specialists use the classification of surgical outcomes of epilepsy treatment proposed by Jerome Engel in 1993 [29]. In accordance with it, 4 classes are distinguished. Despite the widespread use of this classification among neurosurgeons and neurologists throughout the world, it has a number of shortcomings and needs to be revised regarding the clinical assessment of the outcomes of surgical treatment. Thus, in this classification, class I includes both the complete absence of attacks and the persistence of focal attacks, and this group also takes into account the recurrence of attacks after the discontinuation of AEDs. There is also no differentiation by attack types and no display of the dynamics of attack frequency relative to the period before surgical treatment. Therefore, ILAE (2001) proposed a draft of a new classification of surgical treatment outcomes that takes into account clinical and anamnestic data [30] (Table 2). However, many authors use both classifications in their studies. According to the results of 389 resection operations performed by B. Mathon et al. (2017) obtained comparable results using both selective amygdalohippocampectomy and anterior temporal lobectomy. The authors achieved the



Engel I outcome in 83.7% of cases, of which Engel Ia – was found in 57.1% of patients. The first histological type was found in 75.3% of patients, the second type – in 18.7 %, the third type – in 1.2% of patients. In 70% of cases (62–83%), long-term absence of attacks after resection surgery was noted [31]. In the study by Ç. Özkara et al. (2007) analyzed the results of 165 cases of open surgical interventions, among which 138 patients underwent selective resection via the transsylvian approach, and 27 patients underwent anterior temporal lobectomy. The results were assessed using the Engel and ILAE scales. The outcome according to Engel I by the end of the observation was noted in 72.1%, ILAE class Ia – in 52.7%. The period without auras and attacks by the end of the 2nd year, 5 and 8 years after the operation lasted in 89.6, 78.8 and 62.5%, respectively. Discontinuation of antiepileptic therapy was achieved in 41 patients. Complications in the form of hemiparesis were diagnosed in 4 patients, aphasic disorders – in 2 people [32].

In a study by Russian authors (V.V. Krylov, A.B. Gekht , I.S. Trifonov et al ., 2016), who studied the results of resective surgery in 59 patients using the Engel scale , class I outcomes were observed in 69% of patients, of which Engel I was achieved in 42%, class II outcomes were observed in 19% of patients, and unfavorable outcomes were noted in 12% of cases. The most common complication of these types of operations was hemianopsia (62.7%), which in most cases did not bother patients [33]. According to another study (V. R. Kasumov, V. P. Bersnev, R. D. Kasumov , 2011), in patients with drug-resistant epilepsy, divided into groups depending on the type of surgical treatment methods used (transcortical selective mygdalohippocampectomy and selective amygdalohippocampectomy, supplemented by subpial transections in the functionally significant zone), the effectiveness of surgical treatment with a combination of transcortical selective amygdalohippocampectomy and multiple subpial transections was significantly higher than with isolated transcortical selective amygdalohippocampectomy. The combined use of the above-mentioned surgical treatment options allows for positive treatment results in 77.8% of cases, while with isolated selective transcortical amygdalohippocampectomy they account for 66.7% of observations [34]. A frequent complication after surgical interventions for MVC is a violation of the visual fields. In most cases, as a result of damage to the Meyer loop (the temporal part of the optic radiation), superior quadrant hemianopsia develops. In a study by B. Schmeiser et al. (2017) assessed the visual fields in 276 operated patients, revealing visual field impairments in 73% of cases. Significant impairments in everyday life (e.g., difficulty driving a car, crossing the road, reading) were found in 46% of patients. This defect was least common when choosing a subtemporal approach [35]. In 2016, a meta-analysis of surgical treatment of temporal lobe epilepsy performed using stereotactic radiosurgery. The study was based on 13 scientific papers, including a total of 165 cases of surgical treatment with subsequent observation of patients in the range from 6 months to 10 years. In this study, the Engel I result was interpreted as the absence of seizures. On average, by 14 months after surgery, the Engel I result was achieved in 50.9% of patients [36]. Other SRS outcomes were not published in this study. In our country, this method of treating epilepsy has begun to be used relatively recently. According to domestic studies (V.V. Krylov, V.A. Rak, A.S. Tokarev, 2021), all patients operated on using stereotactic radiosurgery had previously undergone amygdalohippocampectomy. In patients with hippocampal sclerosis, the target of the



intervention was the residual fragments of the amygdala , the anterior 2/3 of the hippocampus and the underlying parahippocampal gyrus. Class I outcome according to the J. Engel scale was observed in 1 patient (12.5%). In 4 patients (50%), the outcomes corresponded to class II: IIA - 1 patient, IIB - 2 patients, IIC - 1 patient, unfavorable outcomes were observed in 3 patients (37.5%). The main type of complications when using this technique is radiation necrosis, which can subsequently form a new epileptogenic focus [37]. According to another domestic study (V. R. Kasumov , 2009), when using stereotactic destruction of the hippocampal -amygdaloid complex, a decrease in the number of seizures was noted in 60% of cases [38]. The quality of life of patients after SRS is better than after microsurgery, but the delayed therapeutic effect in case of ineffective intervention and ongoing seizures can be accompanied by a significant deterioration in the patient's condition [39]. Among the specific complications of SRS, the main ones are visual field impairment (17.9%) and aphasic impairments such as acoustic amnesic aphasia (14.9%) [36]. Laser interstitial thermal therapy involves the use of laser light to heat and destroy the affected tissue under the control of MR thermography . With the help of MRI, it is possible to observe the ablation zone with a diameter of 5 mm to 20 mm [40]. B. Youngerman et al . (2020) described the outcomes of the MgLiTT technique in an analysis of 13 scientific papers that included 519 cases . Patients were followed for at least 1 year. The absence of seizures with laser amygdalohippocampectomy was achieved in the range from 36 to 62% of cases . The largest study, including 562 patients with hippocampal sclerosis operated on using the MgLiTT technique , shows an Engel I result of 58 % [41]. These studies demonstrate a comparatively worse result with MgLiTT than with open resection techniques. Practice shows that some patients do not agree to open surgery due to the upcoming trepanation and wide resection, despite the progressive course of the disease. In such cases, according to R. Gross et al . (2015), R. Wicks et al . (2016), the chance to improve the patient's quality of life with minimally invasive techniques should be used. The risk of acoustic-mnesic aphasia in laser hippocampectomy is lower than in resection surgeries . J. Kang et al . (2015) indicate that with this technique, verbal memory impairment will manifest itself more often while maintaining the contextual nature of memorization [42]. The cognitive state of patients after the intervention was also comparatively better than with resection surgery [40]. The most common complication (3–9% of cases) in laser hippocampectomy was contralateral upper quadrant hemianopsia. Summarizing the positive qualities of MgLiTT, we can note low invasiveness, a small number of serious complications, a low probability of cognitive decline in the patient, the possibility of repeating the surgery and rapid recovery of patients after the intervention [42]. The goal of radiofrequency thermocoagulation under stereo -EEG navigation is the destruction of the epileptogenic focus using a radiofrequency generator. SEEG- guided RFTC is usually used in hippocampal sclerosis, FCD, tuberous sclerosis [43]. Analysis by H. Catenoix et al . (2018) demonstrates the outcomes of destruction without using the Engel scale. The work assessed 251 cases of drug-resistant epilepsy for the period 2004–2013. Complete freedom from seizures during the first year was achieved in 23% of patients (pooled indicator). Improvements were achieved in 68% of operated patients [43]. Neurological deficit was 2.5% of cases. Obviously, the outcomes of resection surgeries are much better, but SEEG- guided RFTC can be the method of choice in cases of drug - resistant



epilepsy when open surgery is not possible. The outcomes of surgeries in patients who underwent invasive EEG monitoring as part of preoperative diagnostics show some differences depending on the chosen technique. The outcomes of Engel class I surgeries were noted in 57.3 % of cases using subdural electrodes. Complete relief from seizures was achieved in 55.9% of patients. When using deep electrodes, Engel class I was observed in 71.6% of patients, and a seizure - free period after surgery was observed in 64.7% of cases. Thus, the use of stereo-EEG has proven to be a more accurate method for verifying an epileptogenic focus compared to the use of subdural electrodes [44]. L. Willems et al . (2019) in a group of 18 patients (168 electrodes were used) who underwent stereo-EEG, calculated that the risk of severe complications (bleeding, edema, infection) increases by 1.2% with each new electrode.

Complications such as headache, subfebrile fever can occur 4.2% more often [45]. With the development of neuroimaging, electrophysiological and genetic research methods, the issues of epilepsy, as well as the effectiveness of surgical treatment and its outcomes, are becoming increasingly relevant.

In the updated classification of epileptic syndromes (ILAE, 2017), the term "symptomatic epilepsy" is replaced by "structural epilepsy", which suggests a personalized approach to verifying the epileptogenic zone. This leads to a more favorable outcome of the disease and a reduced risk of relapse when therapy is discontinued. At present, there are sufficient methods for diagnosing MIS, which makes it possible to standardize and introduce into clinical practice in drug-resistant epilepsy a universal algorithm for performing preoperative verification of the epileptogenic zone. Using non - invasive diagnostic methods (careful collection of anamnesis, seizure semiology, video-EEG monitoring, high - resolution MRI , PET/CT with glucose), and if there is insufficient information, resort to invasive methods implantation of subdural electrodes or stereo-EEG). Depending on the surgical technique used, the outcomes of operations can vary significantly. Resection surgery is preferable, since it has the most favorable outcomes in terms of getting rid of seizures and the possibility of subsequent cancellation of drug therapy. However, its disadvantages include the risk of developing neurological and cognitive deficit. Minimally invasive methods are often used, the essence of which lies not so much in the destruction of the epileptic focus as in its disconnection from neighboring structures. This technique is preferable in young patients with MBC of the dominant hemisphere due to a lower percentage of postoperative complications. Surgical treatment of resistant epilepsy in MBC in most cases leads to an improvement in the quality of life of patients. Awareness of possible options for providing care to patients with drug-resistant epilepsy, including the outcomes of surgical treatment, should facilitate adequate decision-making on the tactics of treating the patient.

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