



UNSATISFACTORY OUTCOMES OF SURGICAL TREATMENT OF DRUG-RESISTANT EPILEPSY: ANALYSIS OF CAUSES AND WAYS TO OPTIMIZING TREATMENT

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ABSTRACT

The relevance of the problem under study is due to the high prevalence of drug-resistant epilepsy, an increase in the detection of structural lesions in its etiology and an expansion of indications for surgical treatment.

The purpose of the article is to study the causes of unsatisfactory effectiveness of surgical treatment of drug-resistant epilepsy in the adult population from the standpoint of an interdisciplinary approach in order to determine the ways of comprehensive optimization of treatment results.

Material and methods. The leading approach to the study of this problem is a retrospective open cohort study of surgical treatment outcomes in 36 patients with analysis of adverse outcome factors in 14 individuals.

Results. It was revealed that unsatisfactory outcomes of surgical treatment of epilepsy are due to a combination of reasons. Disease features were the main cause of adverse outcome in 100% of cases, irrational pharmacotherapy additionally complicated the course of the disease in 86% of cases, and surgical reasons in 36% of cases.

Conclusions. Unsatisfactory outcomes of surgical treatment of epilepsy are due to a combination of reasons. An interdisciplinary approach to the problem, improved organization of epileptological care, and further studies of predictors of outcomes of surgical treatment of epilepsy are required. The materials of the article may be useful for developing a personalized approach to the surgical treatment of epilepsy.

Relevance. According to WHO, about 65 million people suffer from epilepsy and the proportion of the general population with active epilepsy (i.e. with ongoing seizures or the need for treatment) currently ranges from 4 to 10 per 1000 people. Drug treatment of epilepsy is currently effective in 70-80% of cases. In the remaining 20-30% of cases, doctors are faced with a drug - resistant form of epilepsy, in which the severity, frequency of seizures, neurological and mental symptoms, as well as the side effects of drugs cannot be satisfactorily corrected and are unacceptable for the patient and (or) his relatives [1]. In these cases, surgical treatment of



epilepsy becomes the method of choice. Surgical treatment of epilepsy brings significant improvement in 65-80% of cases [2]. However, in at least 15% of cases, the outcomes of surgical treatment are unsatisfactory: the frequency and severity of seizures remain at the preoperative level or increase [3]. Specialists identify several predictors of a favorable outcome of surgical treatment: a shorter duration of ineffective therapeutic treatment, a more thorough presurgical examination of patients [4]. With a disease duration of more than 30 years, the probability of complete seizure control after surgical treatment decreases to 60-62% [5, 6]. An important role is played by the appointment of rational pharmacotherapy before and after surgery. Epilepsy treatment is an interdisciplinary problem dealt with by neurologists, psychiatrists, and neurosurgeons with the participation of neurophysiologists therefore, the analysis of cases of unsatisfactory surgical treatment of epilepsy should be carried out by a team of specialists. The search for the causes of unsatisfactory outcomes of surgical treatment and their correction will allow: to improve the quality of life of patients with epilepsy, to reduce the incidence and progression of concomitant somatic diseases, cognitive and mental disorders, the risk of injury, the risk of "unexpected, sudden death in a patient with epilepsy" (SUDEP) [3], and also to reduce the economic costs of the family and the state for the maintenance of a patient with progressive disability [7, 8]. However, little attention has been paid to a comprehensive analysis of the causes of insufficient effectiveness of surgical treatment in the scientific literature [3], and the gender aspects of pharmacoresistance in neurosurgery are insufficiently studied [8]. In such conditions, the search for ways to optimize the surgical treatment of epilepsy has not been sufficiently developed. The aim of the work is to study the causes of low effectiveness of surgical treatment of pharma - resistant epilepsy in the adult population from the standpoint of an interdisciplinary approach in order to determine the ways of comprehensive optimization of treatment results. Material and methods The study is retrospective, open, analytical. To ensure the representativeness of the sample, the directional selection method was used. At the first stage, the primary material of the database of epilepsy patients operated on our clinic was analyzed.

The study was approved by the Ethics Committee. The patients signed informed consents. The inclusion criteria for the study were: – Age over 18 years – Lesional and non-lesional forms of epilepsy lasting more than 3 years; – Focal epilepsies – Drug-resistant epilepsies (DRE) according to the criteria of the International League Against Epilepsy. Exclusion criteria: – Structural epilepsy caused by a space -occupying lesion of the brain (tumors, vascular malformations) with dominance of symptoms of the space-occupying process. Children under 18 years of age At the second stage, interviews and questionnaires were conducted among patients to study the outcomes of surgical treatment of drug-resistant epilepsy and to assess the dynamics of the disease after surgery. The questionnaires were administered to patients who had undergone surgery at least 1 year ago. Questionnaire conditions: the patient or his close relative answered questions from a specially developed questionnaire, "Outcomes of Surgical Treatment of Epilepsy," concerning the patient's physical and psychological condition, the number, quality, and nature of changes in epileptic seizures at present, and the regimen of anticonvulsant therapy. Most often, the questionnaires took the form of telephone interviews with simultaneous completion of the questionnaire by the research physician, since many patients lived in other regions and neighboring countries. To



verify the condition, we additionally used data from the latest electroencephalographic studies (EEG) video EEG monitoring (VEM) and magnetic resonance imaging (MRI) of the brain. The outcomes of surgical treatment were assessed according to the classification of outcomes of surgical treatment of epilepsy of the International League Against Epilepsy (ILAE). Unfavorable outcomes include classes 5 and 6 of the scale. A comprehensive interdisciplinary analysis of the causes of unsuccessful surgical treatment was conducted with the involvement of neurosurgeons, neurologists, and neurophysiologists. In the course of the interdisciplinary analysis, the main and additional causes of ineffective surgical treatment of epilepsy were identified in each clinical case. Descriptive statistics methods were used to collect information and present the results.

Results. The final sample of the first stage consisted of 91 medical histories of patients with drug - resistant epilepsy. By gender, men predominated — 59.3% (54/91; 59.3%), fewer women were operated on — 40.7% (37/91; 40.7%). The male:female ratio was 1.5 :1. In the pilot study of the second stage, patients and their relatives were interviewed.

Two patients dropped out (relatives found out that the patients died: in one case, a completed suicide, the other patient died as a result of a traffic accident). The results of surgical treatment were assessed in accordance with the ILAE classification of outcomes (Table 1). Unfavorable outcomes of surgical treatment were analyzed in 14 people. These patients had classes 5 and 6 on the ILAE scale. The outcome of surgical treatment was assessed using the ILAE scale in most cases 2-3 years after surgery (10 patients (10/14; 71%) and only in 4 patients (4/14; 29%) 1 year after surgery. The analysis of gender distribution revealed a predominance of men (9/14; 64%) over women (5/14; 36%). The age of patients ranged from 20 to 68 years, with a predominance of patients aged 20-30 years. The average age was 34 years. The analysis of the causes of unsuccessful surgical treatment was performed by an interdisciplinary team using the following parameters:

1. Features of the clinical course of epilepsy:
 - a. Etiology of the disease
 - b. Duration of the disease
 - c. Type and course of epilepsy
 - d. Presence of polymorphic and bilateral (secondarily generalized) seizures
 - e. Typology and prevalence of changes in clinical and instrumental studies
2. Features of surgical treatment
 - a. Incomplete removal of the epileptic focus
 - b. Palliative surgery for epilepsy
 - c. Repeated surgeries for epilepsy
3. Features of antiepileptic therapy
 - a. Rational and adequate therapy
 - b. Monotherapy in drug -resistant epilepsy
 - c. Low doses of AEDs
 - d. Irrational polytherapy

In each clinical case, the causes of unsatisfactory outcomes were analyzed and identified (Table 2). In each case, the main and additional causes of unsatisfactory outcome were identified. In the group of main causes, the features of the clinical picture of epilepsy prevailed.



Less often, the main cause was surgical causes, in isolated cases - irrational antiepileptic therapy. Electroencephalographic changes were not the main reasons for unsuccessful surgical outcomes, but they served as additional reasons for low treatment efficiency. Among the additional reasons, irrational antiepileptic therapy prevailed. The characteristics of the disease were the main reason for an unfavorable outcome in 100% of cases, irrational pharmacotherapy additionally complicated the course of the disease in 86 % of cases, and surgical reasons in 36 % of cases. When assessing the lateralization of the epileptic focus, a predominance of negative outcomes was revealed in operations on the right hemisphere (69%) compared to the left - sided lateralization (31 %). Peculiarities of epilepsy influencing the outcome of surgical treatment were revealed in 100% of cases. Duration of the disease ranged from 3 to 33 years. Only 3 people suffered from epilepsy for less than 10 years. In 3 patients, the duration was more than 30 years. In most cases, it was over 20 years. The average duration in the group up to 10 years was 5.7 years, in the group with a disease duration of more than 20 years - 25.9 years. The onset of the disease was in adulthood only in one case. Basically, the onset occurred in childhood and dominated in the puberty period.

The etiology of epilepsy influenced the outcome of surgical treatment more often due to the extensiveness of the structural lesion and the impossibility of removing the epileptic focus in a functionally significant zone. Post -traumatic epilepsy was dominant - 5 people (5/14; 36%), in second place were malformations of the central nervous system - 3 (3/14; 22%), infectious and perinatal lesions CNS were noted in the same quantity - in 2 people (2/14; 14%). MR-negative epilepsies were confirmed in 2 people (2/14; 14%). Seizures in the early postoperative period were noted in 3 people (3/14; 22%). In female epilepsy, catamenialism was noted in half of the cases, which aggravates the clinical picture and reduces the effectiveness of antiepileptic therapy. Analysis of antiepileptic therapy showed that only in 2 patients the therapy was rational and adequate (2/14; 14%). The structure of irrational therapy included: low doses of antiepileptic drugs (AEDs), AED monotherapy in drug-resistant long - term epilepsy, irrational polytherapy (Fig. 1). Low doses of AEDs predominated, detected in 5 patients (36%). The use of monotherapy in drug-resistant epilepsy was noted in 4 patients (4/14; 29%). Irrational polytherapy (use of two AEDs with the same mechanism of action) was detected in 3 patients (3/14; 21%). Thus, it should be noted that the use of rational AED regimens was the rarest. Thus, the conducted analysis showed the complexity of the reasons for unsatisfactory outcomes of surgical treatment of drug-resistant epilepsy.

Discussion: Today, the goal of surgical intervention in epilepsy is: complete cessation of seizures or a significant reduction in their frequency and severity, improvement of social, labor and pedagogical adaptation, improvement of the quality of life with minimal negative consequences, in any case less significant than the predicted improvement in the patient's condition [7]. The work is devoted to an important problem of surgical treatment of epilepsy - the study of the cause of low efficiency of surgical treatment of drug-resistant epilepsy from the position of an interdisciplinary approach and determination of ways of complex optimization. The assessment of treatment outcomes was carried out according to the classification of outcomes of surgical treatment of epilepsy ILAE, according to which classes 5 and 6 are considered unfavorable. It should be noted that this classification has a drawback concerning class 5, which combines a wide range of results. One class combines



both a 50% decrease in the initial frequency of days with seizures and an increase in the initial frequency of days with seizures to more than 100%. This also includes the lack of dynamics in the frequency of seizures. It is advisable to divide patients taking into account insufficient effect, its absence and deterioration of the condition. Changes in the requirements for assessing the effectiveness of drug therapy, the achieved successes of conservative treatment dictate a change in the approach to assessing surgical treatment methods, universalization of assessments of treatment methods.

Analysis of the obtained data shows that mainly patients who underwent surgical treatment in the Institute's clinic had a very long history of the disease: the average duration of the disease before surgical treatment is 19.4 years. This category of patients is characterized by aggravation and progression of the course of epilepsy with such a long course of the disease, especially against the background of the ineffectiveness of drug treatment. A similar study conducted by Berg AT in 2004 revealed the duration of the period from the diagnosis of epilepsy to surgery in adults to be on average about 20 years [9]. The past 14 years have not affected the change in the situation. According to the study by V.V. Krylov et al. (2016), the average duration of the period from the onset of the disease to surgical treatment is 19.2 years. At the same time, about 75% of such patients did not know about the possibility of surgical treatment [3]. When analyzing the etiology of epilepsy in cases of unsatisfactory outcomes of surgical treatment, the etiological diagnosis was not deciphered in 2 cases. The problem of MR-negative epilepsies is relevant in modern studies, taking into account the fact that the chance of "complete control" over seizures in patients with MR-positive forms is 2.5–2.8 times higher than with MR-negative ones [6]. Surgical treatment of drug-resistant epilepsy is only a stage of complex therapy of the disease, which, from a modern standpoint, involves taking antiepileptic therapy for at least 5 years after surgery. However, an analysis of the drug therapy performed showed unsatisfactory antiepileptic support. The most common reason for irrational pharmacotherapy was low doses of AEDs. Almost a third of patients (4/14; 29%) were retrospectively diagnosed with AED monotherapy for long-term drug-resistant epilepsy. The problem of determining ways to comprehensively optimize treatment results should be considered from the standpoint of an interdisciplinary approach. Reducing the duration of the disease before surgical treatment is a matter of interaction between neurologists and neurosurgeons. When identifying the structural etiology of epilepsy, which is an independent comorbid disease, such as cavernous angioma of the brain, the question of surgical treatment should be raised earlier [10]. Not only presurgical diagnostics, but also pre-surgical preparation with the appointment of rational antiepileptic therapy. Fulfillment of these tasks requires organizational restructuring of care for patients with epilepsy - the creation of highly equipped epileptological centers with neurosurgical hospitals. Thus, the analysis of the causes of unfavorable outcomes of surgical treatment of drug-resistant epilepsy made it possible to identify factors that negatively affect the outcome of surgical intervention. The duration of the disease aggravates the course of epilepsy and reduces the effectiveness of surgical treatment. Irrational AED therapy is not sufficiently taken into account as a factor in unfavorable outcomes. Correction of antiepileptic therapy should be carried out at the stage of pre-surgical preparation, a stable AED regimen should be at least 3 months



before surgery. It is necessary to improve the quality of diagnostics for accurate localization of the epileptic focus.

Conclusions

Unsatisfactory outcomes of surgical treatment of drug-resistant epilepsy in the overwhelming majority are due to severe forms of drug - resistant epilepsy in neurosurgical patients. Additional factors are irrational antiepileptic therapy and features of surgical intervention. The main directions for increasing the effectiveness of surgical treatment of drug - resistant epilepsy are a comprehensive interdisciplinary approach to the problem, improving the organization of epileptological care, and further studies of predictors of outcomes of surgical treatment of epilepsy. The materials of the article can be useful for determining a personalized approach to the treatment of neurosurgical patients.

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