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Presurgical evaluation algorithm of epilepsy and its practical significance

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Objective: Evaluation of the efficacy of surgical treatment for different forms of epilepsy using individualized complex presurgical diagnostic algorithms.

Materials and Methods: The study included 104 patients with localized unifocal forms of epilepsy and 48 patients with multifocal epilepsy. Among them, 68 (44.7%) were children and 84 (55.3%) were adults. Patients' age ranged from 2 to 63 years. All patients had frequent epileptic seizures and unsatisfactory results of medical treatment. Recurrent status epilepticus or serial seizures in the anamnesis were presented in 74 cases (48.7%). Medication for all patients before surgery treatment included from 1 to 8 antiepileptic drugs. Postsurgical follow-up lasted from 4 months to 16 years. Main examinations included: complete medical history, types of epileptic seizures, EEG or video-EEG, brain MRI. Additional examinations included: MRI - tractography and functional MRI, single-photon emission computed tomography (SPECT), positron emission tomography, subtraction ictal SPECT co-registered to MRI, and intraoperative corticography.

Results: The use of presurgical evaluation algorithm made it possible to localize epileptogenic foci (EF) in all patients. The method of surgical intervention was chosen only of the received preoperative data. Seizures free (Engel Ia) was achieved in 67 (44.1%) patients. Single focal or nocturnal seizures (Engel Ib-c) were reported in 37 (24.3%) patients. Significant regression of the number of epileptic seizures (Engel II) was achieved in 28 (18.4%) cases, and moderate regression (Engel III) - in 12 (23.1%) patients. Absence of positive dynamics after surgery (Engel IV) occurred in 7 (4.6%) patients. Surgical complications occurred in 13 (8.6%) patients.

Conclusions: Presurgical evaluation algorithm helped localize unifocal and multifocal EF, which allows choosing a surgical technique, accurately planning the strategy of intervention and carrying it out safely. In cases of surgical impact on EF, it is possible to achieve complete seizure control.

Key words: *epilepsy; hemispherotomy; epilepsy surgery; cortical dysplasia*

Introduction

In recent years, numerous technological advances in both diagnostic and therapeutic procedures for epilepsy have increased the number of patients who may be candidates for surgical treatment, which can improve their quality of life. The rapid development of modern technologies requires constant updating of epilepsy treatment algorithms. The main strategy of in-depth preoperative diagnosis of structural epilepsy involves the use of non-invasive techniques, if necessary - examination and use of invasive techniques [1]. This approach allows effective resection interventions, functional disconnections and neuromodulation surgeries. The current stage of epilepsy surgery is characterized by the development of minimally invasive diagnostic and ablation procedures (laser interstitial thermal therapy (LITT), stereotactic radiosurgery (SRS), focused ultrasound destruction and classical radiofrequency ablation) and the introduction of non-destructive methods neurostimulation (responsive neurostimulation (RNS)), deep brain stimulation (DBS),

vagus nerve stimulation (VNS). Among diagnostic procedures, stereoelectroencephalography with depth electrodes (stereoelectroencephalography (SEEG)) has become widespread. Despite the introduction of new types of neurosurgical interventions, specialists face difficulties in choosing an individual diagnostic and treatment strategy.

About 30% of patients with epilepsy remain drug-resistant, despite the use of modern antiepileptic drugs (AEDs) [2-4]. According to the definition of the American Academy of Neurology and other North American and international organizations, patients who cannot get rid of seizures when using two or more AEDs are resistant to drug treatment [5-7]. Prescribing additional AEDs may be inappropriate due to the extremely low efficacy of epilepsy polytherapy (4-14%) and the high probability of adverse reactions [7-10]. Patients with epilepsy with low treatment efficacy against the background of AEDs monotherapy or polytherapy should undergo a non-invasive pre-surgical evaluation (mandatory and additional examination methods, consultation of

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a professional team (neurologist, neurophysiologist, neurosurgeon, neuropsychologist, neuroradiologist)). The ultimate goal of epilepsy treatment is seizure freedom, which is the most preferred quality of life measure [10].

The purpose of the pre-surgical evaluation is to determine the type of epilepsy, the localization of the epileptogenic focus (EF), the pathways of spreading epileptogenic activity and the possibility of effective surgical treatment of the patient. The diagnostic algorithm involves establishing a complete medical history, assessing the patient's neurological and physical status, a detailed study of the semiology and frequency of seizures, the duration and symptoms of epilepsy, as well as risk factors [11]. At this stage, three levels of epilepsy according to the current International League Against Epilepsy (ILAE) must be determined: types of seizure, form of epilepsy, epileptic syndrome [12] (**Table 1**). All types of epileptic seizures should also be determined [13] (**Table 2**). A comprehensive neuropsychological assessment makes

it possible to localize the symptomogenic zone and evaluate parameters of neurocognitive activity which may be affected by certain surgical interventions [14].

The main neurophysiological research methods are electroencephalography (EEG) and long-term video EEG monitoring, to detect epileptic activity of the brain and clarify the anatomical localization of EF (**Fig. 1**) [15].

High-field magnetic resonance imaging (MRI) is also an important method, since anatomical identification of focal lesions that corresponds to EF significantly increases the likelihood of successful surgical treatment (**Fig. 2**) [16, 17]. Modern MRI devices with a magnetic field strength 3 T and more and the development of epilepsy-specific modes increase the incidence of anatomical lesion (**Fig. 3**) [17, 18]. MRI tractography can also play an important role in preparing for surgery in epilepsy, which allows not only to identify the leading pathways of functionally significant brain regions (**Fig. 4**), but also to plan the plane of functional disconnection of the affected epileptogenic zone (**Fig. 5**). Interictal magnetocephalography (MEG) can be a useful tool

Table 1. ILAE epilepsy classification scheme [12]

Comorbidity	Type of seizures				Etiology
	Focal	Generalized	Unknown onset		Structural
	Type of epilepsy				Genetic
	Focal	Generalized	Combined generalised and focal	Unknown	Infectious
	Epilepsy syndromes				Metabolic
					Immune
				Unknown	

Table 2. The basic ILAE 2017 operational classification of seizure types [13]

Classification of epileptic seizure types					
Focal onset		Generalized onset		Unknown onset	
Aware	Impaired awareness	Motor: Tonic-clonic Other motor Nonmotor (Absence)		Motor: Tonic-clonic Other motor Nonmotor (Absence)	
Motor onset				Unclassified	
Nonmotor onset					
Focal to bilateral tonic-clonic					

for localization of epileptogenic spiking activity that corresponds to the irritation area, which may also contain EF [19]. However, interpretation of MEG data may be impossible in patients who have infrequent seizures. In one study, changes were evaluated in about 78% of 132 patients. They corresponded to the predictable EF in two-thirds of these individuals [19]. In addition, MEG and functional MRI (fMRT) can be useful for non-invasive localization of language

centres, surgical planning and risk prediction (**Fig. 6**) [20]. Functional MRI is also used for lateralization of verbal and visual-spatial memory in some clinics, but the need to repeated tasks makes the localization of memory centers more complex than identifying functional language or sensorimotor areas [20]. You can perform an invasive test that allows you to find out the lateralization of memory and language centres [21].

This article contains some figures that are displayed in color online but in black and white in the print edition.

Interictal positron emission tomography (PET) is also a valuable diagnostic procedure, as a focal area of hypometabolism can help confirm the localization of EF and predict a favorable surgical outcome [22,23]. For example, anteromedial temporal lobe hypometabolism can often be seen on a normal MRI, but this change on PET can clearly correspond to EF. Temporal lobectomy with amygdalohippocampectomy can relieve these patients from seizures, the most common cause of which is cortical malformations or mesial temporal sclerosis [24]. In cases where bilateral mesial temporal sclerosis is suspected according to MRI data, PET is one of the main techniques for determining the lateralization of the epiactive mesial complex of the temporal lobes (**Fig. 7**).

Additional methods of diagnosing an epileptogenic focus can be used. Ictal single-photon emission computed tomography (SPECT) may be useful in identifying the area of hyperperfusion corresponding to EF. It is also possible to exclude the interictal image

from SPECT and further process information on MRI using the SISCOM technique (Subtraction ictal SPECT co-registered to MRI) [25]. SISCOM can have a high diagnostic value as PET, but this technique is more complex and resource-intensive procedure [26].

In cases where non-invasive techniques fail to accurately establish EF, an option for further examination is invasive EEG monitoring, which aims to obtain ictal and interictal electrographic data. The procedure involves a surgical procedure (electrodes implantation) and monitoring for several days in a specialized department. Two main methods of invasive EEG are currently used: implantation of subdural (subdural electrode recording (SDE)) or depth (SEEG) electrodes. The SDE technique involves performing a wide craniotomy and placing subdural electrodes in the form of grids or strips on the surface of the cerebral cortex. Instead, the SEEG procedure is performed without a craniotomy using stereotactic techniques and

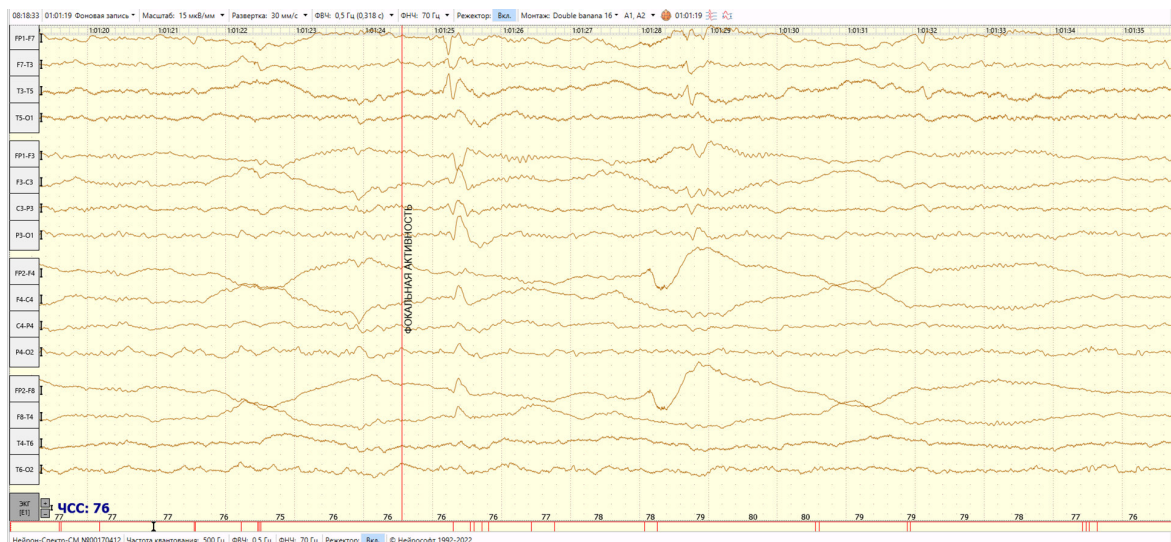


Fig. 1. Daily video EEG monitoring. Focal epileptiform activity in the left frontotemporal region (own observation)

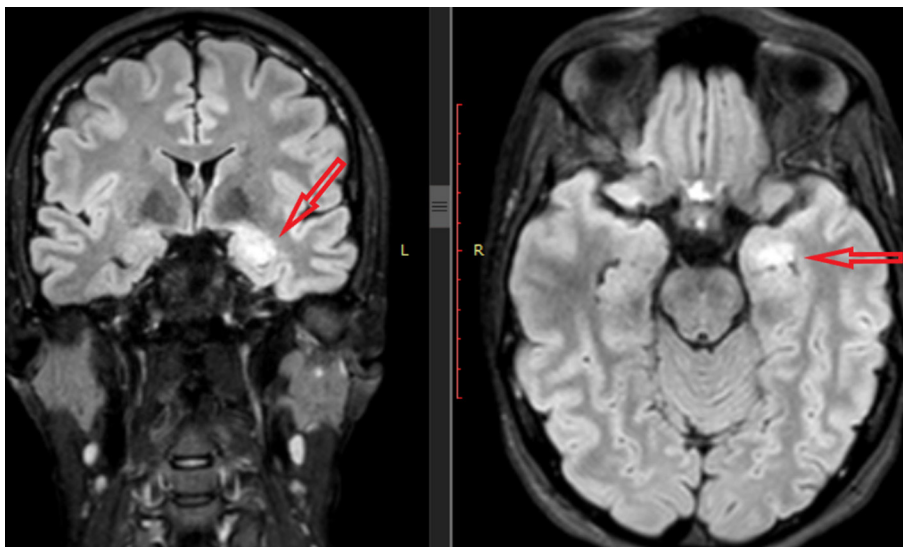


Fig. 2. MRI (3 T) of the brain according to "epilepsy" protocol (sections on the anatomical axis of hippocampus). Mesial temporal sclerosis on the left (own observation)

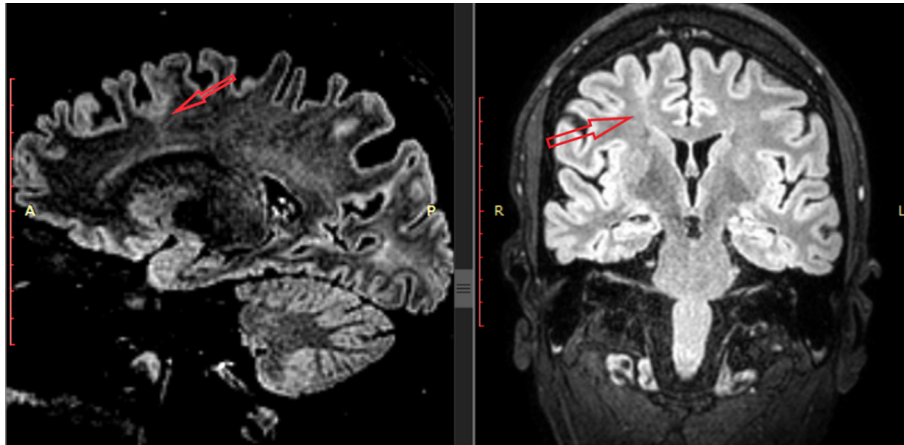


Fig. 3. MRI (3 T) of the brain according to the protocol "epilepsy". Focal cortical dysplasia (IIB type by Blumcke classification) right frontal lobe (own observation)

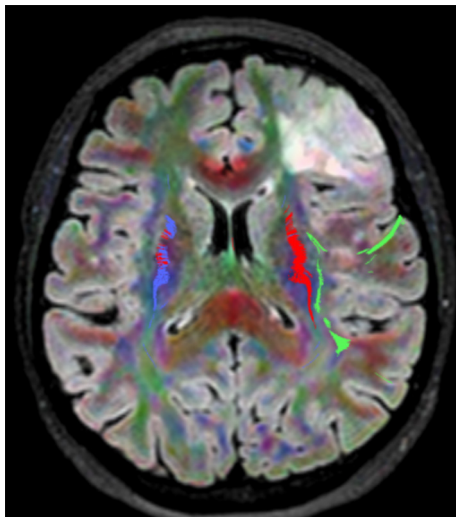


Fig. 4. MRI tractography. Intracerebral tumor of the left frontal lobe (histologically – anaplastic oligoastrocytoma, Gr III). Green color - fasciculus arcuatus, Reil's band, red - corticospinal tract (own observation)

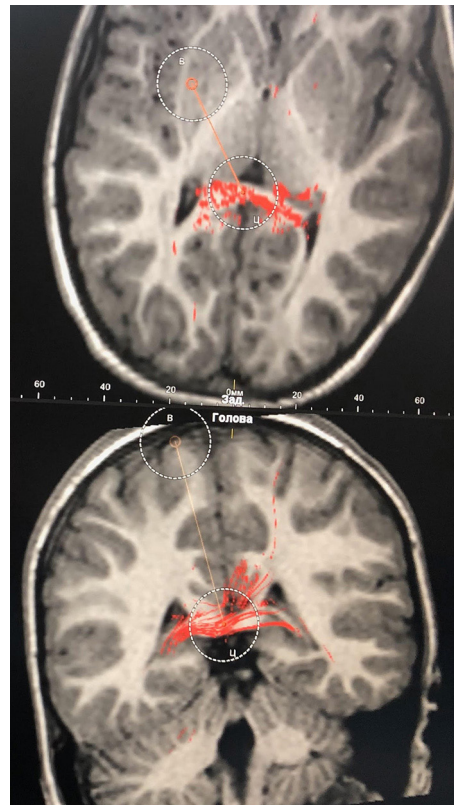


Fig. 5. MRI tractography. Condition after anterior callosotomy 18.03.20. Preserved commissural fibers are visualized in the area of the corpus callosum splenium (own observation)

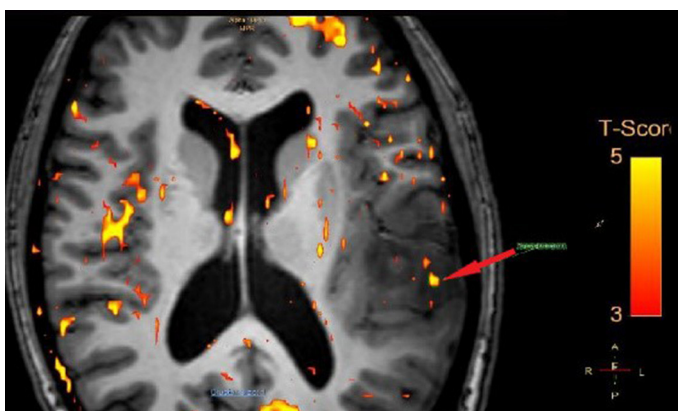


Fig. 6. MRI (3 T) of the brain. Intracerebral tumor of the left temporal lobe (histologically – anaplastic astrocytoma, Gr III); fMRI with visualization of language centres (Wernicke's centre - the active signal area from the centre is indicated by an arrow) (own observation)

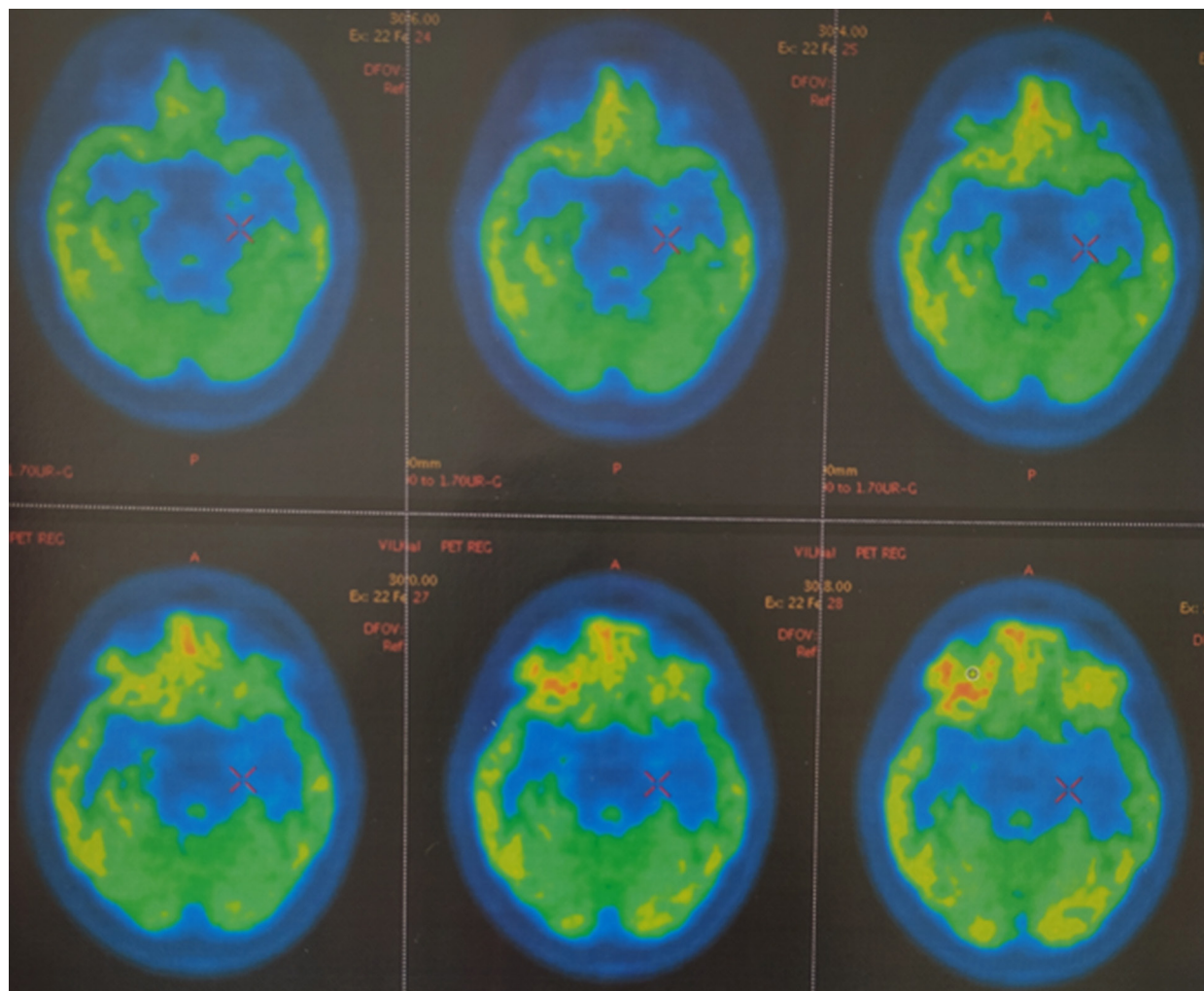


Fig. 7. PET of the brain: signs of hypometabolism in the area of the left hippocampus. Mesial temporal sclerosis on the left (own observation)

special depth electrodes. Because electrode coverage is limited, both procedures require assumptions about the possible location of EF and areas of epileptogenic activity. SDE can also be performed during the final surgery to more accurately determine the localization of the EF, the pathways of spreading epileptiform activity, possible localization of functionally significant centres of the cerebral cortex.

SEEG is a minimally invasive technique of implanting electrodes into the deep parts of the brain, during which stereotactic or frameless neuronavigation, a stereotactic robot, a stereotactic frame or an individual disposable frame printed on a 3D printer are actively used [27–29]. The general method was developed in France in the 1950s [30], and has become widespread in Europe and beyond only in recent decades. The main advantage of SEEG is the ability to map in three-dimensional space deep EF and pathways of propagation of epileptogenic activity [31]. If the areas of greatest interest are deeply localized (periventricular or insular areas), then SEEG will provide maximum information. However, coverage by depth electrodes of the superficial parts of the brain is more limited than in SDE [32]. According to the literature, SEEG is associated with reduced severity of

perioperative pain, faster patient recovery, and a lower rate of serious complications (1.3%) [33] compared to SDE (3.4%) [34]. An additional advantage of SEEG is that the procedure for removing the depth electrodes is simple and does not require repeated full surgical intervention as in SDE.

If the case requires careful delineation of EF boundaries in a neocortical area, such as the cortical areas covering or adjacent to speech centres, a combination of craniotomy with corticography or long-term SDE implantation may be better options. This allows coverage of a larger cortical surface area, which will facilitate a more accurate determination of the localization of EF, boundaries and pathways of spreading epileptiform activity (**Fig. 8**). Using SDE, it is possible to map speech centres using direct cortical stimulation during monitoring or surgery. However, it should be taken into account that SDE does not allow mapping of the deep structures of the brain, unlike SEEG. If the SEEG results suggest the EF location in a possible neocortical area, but more detailed cortical mapping is required before definitive treatment, then a second monitoring procedure with craniotomy for targeted SDE placement may be considered. Conversely, after ineffective SDE

procedure, it is possible to perform SEEG of the target structures [35].

Study objective: to evaluate the efficacy of surgical treatment for different forms of epilepsy using individualized complex preoperative diagnostic algorithms.

Materials and methods

Study participants

The study enrolled 152 patients with different forms of epilepsy who were treated in the Department of Functional Neurosurgery and Neuromodulation of the Institute of Neurosurgery named after Acad. A.P. Romodanov, Ukraine. Informed and voluntary written consent to participate in the study was obtained from all patients. The study was approved by the Ethics and Bioethics Committee of the Institute of Neurosurgery named after Acad. A.P. Romodanov, Ukraine (Minutes № 2 dated April 15, 2019).

Criteria for inclusion in the study:

- 1) presence of unifocal or multifocal epilepsy;
- 2) the fact of ineffectiveness of anticonvulsant therapy (pharmacoresistance) and progressive course of the disease was established.

Characteristics of the group

Among the patients, there were 104 (68.4%) patients with localized unifocal forms of epilepsy and 48 (31.6%) with multifocal epilepsy, of whom 68 (44.7%) were children and 84 (55.3%) were adults. Patients ranged in age from 2 to 63 years. All patients had frequent epileptic seizures, a progressive course of the disease, and resistance to AEDs. A history of recurrent status epilepticus or serial seizures occurred in 74

(48.7%) patients. Before surgery, patients took from 1 to 8 antiepileptic drugs (**Table 3**).

Study design

The preoperative examination included examination by a neurologist, epileptologist, neurosurgeon and psychiatrist to determine three levels of epilepsy and types of epileptic seizures in all patients. Additionally, 110 (72.4%) patients underwent a comprehensive neuropsychological assessment. All patients underwent electroencephalography, video-EEG – 71 (46.7%). In our study, video EEG monitoring was performed mainly in cases where after the first EEG there were doubts about the data obtained, in order to obtain more detailed electrophysiological data. Magnetic resonance imaging of the brain on a high-field tomograph of 1.5-3.0 T was performed in all patients, MRI with tractography – 66 (43.4%), fMRI – 13 (8.6%), single-photon emission computed tomography (SPECT) – 35 (23%), PET – 25 (16.4%), SISCOP – 8 (5.3%), invasive intraoperative corticography – 49 (32.2%) (**Table 4**).

According to the results of the follow-up examination in the case of unifocal epilepsy, the following etiological causes were determined: cortical dysplasia - in 16 patients, mesial temporal sclerosis - in 21 patients, gray matter heterotopia - in 9 patients, localized gliosis of the brain - in 6, cavernous malformation - in 13, arachnoid cysts with atrophy of the surrounding brain substance - in 9, brain tumors - in 30. Among the causes of multifocal epilepsy, the following prevailed: perinatal hypoxic-ischemic encephalopathy - in 11 patients, consequences of intracerebral hemorrhage - in 9, widespread cortical dysplasia - in 8, Rasmussen encephalitis - in 6, brain tumors - in 2, consequences of meningoencephalitis - in 7, lissencephaly - in 1, hemimegalencephaly - in 2, Sturge-Weber syndrome - in 2.

The method of surgical intervention was chosen solely on the basis of data obtained on the type of epileptic seizures, localization, number of EF and pathways of spreading epileptogenic activity. The following surgical interventions were performed: in unifocal epilepsy (104 patients) anterior temporal lobectomy - in 21 cases, anterior temporal lobectomy supplemented with amygdalohippocampectomy - in 57 cases, EF topectomy - in 26 cases, in multifocal epilepsy (48 patients) functional hemispherectomy - in 12 cases, stereotactic callosotomy - in 12, microsurgical callosotomy - in 18 (extended anterior callosotomy - in 7, total - in 11), multilobar resections - in 6. Stereotactic interventions were performed using the CRW Radionics stereotactic system (Radionics Inc., USA), calculations coordinates of the destruction target - using FrameLink planning stations, StealthStation (Medtronic, USA) and ELEMENT (Brainlab, Germany).

Postoperative catamnesis was monitored from 4 months to 16 years. Follow-up examinations were performed 3, 6 and 12 months after surgery, and annually thereafter.

Antiepileptic drug therapy was not changed in the first 6 months after surgery.

The effectiveness of surgical intervention was evaluated using the Engel scale.

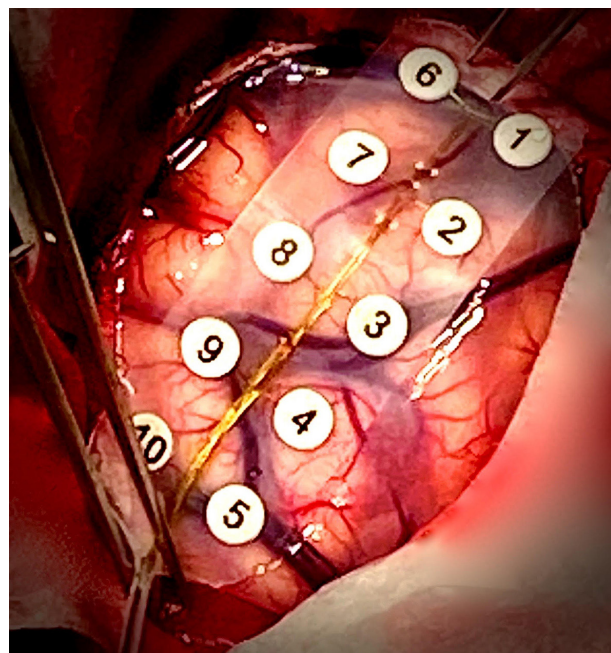


Fig. 8. Intraoperative mapping of the cerebral cortex using subdural electrodes (SDE) (own observation)

Table 3. Clinical characteristics of patients

Indicator	Unifocal forms of epilepsy (n=104)	Multifocal forms of epilepsy (n=48)
Children	31 (29,8%)	37 (77,1%)
Adults	73 (70,2%)	11 (22,9%)
Average age, years	26,8 ± 1,6	12,7 ± 1,9
Mean duration of epilepsy, years	11,7 ± 1,1	8,9 ± 2,3
History of recurrent status epilepticus or serial seizures	36 (34,6%)	38 (79,2%)
Daily seizures	73 (70,2%)	46 (95,8%)
Progressive psychoemotional disorders	29 (27,9%)	34 (70,8 %)
Average number of antiepileptic drugs	2,6 ± 0,4	5,1 ± 2,5

Table 4. Diagnostic methods depending on the number of probable epileptogenic foci

Methods	Unifocal forms of epilepsy (n=104)	Multifocal forms of epilepsy (n=48)	Total (n=152)
Determination of medical history	104 (100,0%)	48 (100,0%)	152 (100,0%)
Determination of epilepsy levels and types of seizures	104 (100,0%)	48 (100,0%)	152 (100,0%)
Comprehensive neuropsychological assessment	75 (72,1%)	35 (72,9%)	110 (72,4%)
EEG	104 (100,0%)	48 (100,0%)	152 (100,0%)
Video EEG monitoring	42 (40,4%)	29 (60,4%)	71 (46,7%)
MRI of brain (1.5-3.0 T) in "Epilepsy" mode	104 (100,0%)	48 (100,0%)	152 (100,0%)
MRI of the brain (3.0 T) in "Multiparametric" mode (with tractography)	44 (43,3%)	22 (45,8%)	66 (43,4%)
fMRI	8 (7,7%)	5 (10,4%)	13 (8,6%)
SPECT	21 (20,2%)	14 (29,2%)	35 (23,0%)
Subtractiion ictal SPECT, coregistered to MRI (SISCOM)	5 (4,8%)	3 (6,3%)	8 (5,3%)
PET	19 (18,3%)	6 (12,5%)	25 (16,4%)
Invasive corticography	23 (22,1%)	18 (37,5%)	41 (26,9%)

Statistical analysis

Statistical processing at the stage of analysis of the clinical characteristics of compared groups was performed using traditional parametric statistical methods. Arithmetic mean value, error of arithmetic mean value and root-mean-square deviation were calculated. <0.05 (5%) was taken as the critical value of the statistical significance level.

Parametric statistical methods were not used due to the difficulty of creating comparable groups in patients with epilepsy according to this clinical feature. The Engel scale is the only clinical assessment scale for patients with epilepsy who have undergone surgery. There are no scales for such assessment of patients at the preoperative stage, hence such statistical assessment was not carried out in our study.

Information on the daily occurrence of seizures and psychoemotional disorders in patients at the pre-surgical stage is given as additional clinical data.

Results and discussion

The use of the above diagnostic algorithm enabled localization of EF in all patients.

Most patients underwent the surgery well. Depending on the type of surgery, patients were activated the next day or one day after the operation. The total number of patients whose seizures stopped (Engel Ia) was 67 (44.1%). Complete control of seizures with auras or single focal seizures in early postoperative period (Engel Ib-c) was recorded in 37 (24.3%) patients, single focal or nocturnal seizures (Engel II) in 28 (18.4%), reduction in the number of seizures (Engel

III) in 12 (23.1%), absence of positive dynamics after surgery (Engel IV) in 7 (4.6%). Thus, effective control over epileptic seizures (Engel I-II) was achieved in 132 (86.8%) patients (**Table 5**).

Surgical complications occurred in 13 (8.6%) patients. A frequent complication was the involvement of the anterior choroidal artery with the development of an ischemic injury in the area of the internal capsule and contralateral hemiparesis in patients who underwent anterior temporal lobectomy with amygdalohippocampectomy (5 (6.4%) patients in the temporal lobectomy group). The frequency of this complication is consistent with the literature. These complications were observed more frequently at the beginning of the introduction of the technique into routine surgical practice - 3 (1.97%) cases in 2006–2012 and 2 (1.31%) cases in 2013–2022. In 3 (1.97%) patients, complications occurred in the form of hemorrhage in the surgical bed: in 2 cases after EF topectomy; in 1 case - after temporal lobectomy with amygdalohippocampectomy. Ischemic dysfunction occurred in 2 patients, who underwent anterior temporal lobectomy followed by amygdalohippocampectomy. These cases did not require repeated surgical interventions. One patient developed a chronic subdural hematoma 5 months after microsurgical callosotomy and required removal. Another patient (0.7% of all patients operated on, 2.1% of patients operated on for multifocal epilepsy) developed hydrocephalus after functional hemispherotomy, which necessitated repeated CFS shunt surgeries. A 4-year-old child had pneumothorax and cardiac arrest during the final stages of functional hemispherotomy. Emergency resuscitation measures were able to restore it. The patient developed posthypoxic ischemic encephalopathy and homeostasis disorder, which led to death 2 months after surgery. The overall postoperative mortality was 0.7%. The need to perform a reoperation due to low effectiveness of seizure control occurred in 6 (3.9%) cases. Two patients, who were previously subjected to stereotactic callosotomy, additionally underwent microsurgical total callosotomy, and four patients underwent anterior temporal lobectomy supplemented with amygdalohippocampectomy. After reoperations, all patients had better seizure control (Engel II).

A significant regression of psychoemotional and cognitive disorders was registered in all patients with the result of Engel I-II surgery.

Currently, the development of diagnosis and treatment of epilepsy is observed. Neuroimaging and electrophysiological research methods are constantly being improved, which, together with the synthesis of the newest AEDs and improvement of surgical interventions and social rehabilitation measures, makes it possible to effectively fight this severe pathology.

The modern development of the medical field in Ukraine makes it possible to use almost all methods of preoperative examination of patients with epilepsy that are generally accepted in the world. Such methods as video EEG monitoring, multiparametric 3.0 T MRI, SPECT and PET are routinely used. MRI tractography, fMRI, SISCOM, corticography can be performed, if necessary. However, the possibilities of invasive diagnostics remain limited. Long-term invasive monitoring is currently not used due to the lack of a material and technical base, insufficient funding, and the high cost of necessary equipment. Many medical problems arise when using invasive methods of examination, which are only diagnostic procedures. The introduction of new methods of surgical treatment of epilepsy requires the mandatory development of diagnostic techniques.

Conclusions

The purpose of the preoperative assessment of patients with epilepsy is to establish the exact localization of a single or multiple EF and determine the possible tactics and type of surgical treatment. Mandatory (basic) preoperative examination of the patient includes: determination of three levels of epilepsy and types of epileptic seizures, electrophysiological (EEG, video-EEG) and neuroimaging (1.5–3.0 T MRI of the brain) examinations. Additional methods can be used to clarify the localization of EF.

The complex of modern diagnostic techniques makes it possible to visualize EF in a large number of patients with epilepsy. High diagnostic informativity can provide not only the possibility of effective surgical treatment, but also its safety in monitoring and preservation of functionally significant centres of the brain. In case of surgical impact on EF, it is possible to achieve complete seizure control, regression of psychoemotional and cognitive disorders and improve the social adaptation of patients.

Table 5. Surgery outcomes

Indicator	Unifocal forms of epilepsy (n=104)	Multifocal forms of epilepsy (n=48)	Total (n=152)
Score on the Engel scale:			
Ia	44 (42,3%)	23 (47,9%)	67 (44,1%)
Ib-c	29 (27,9%)	8 (16,7%)	37 (24,3%)
II	20 (19,3%)	8 (16,7%)	28 (18,4%)
III	7 (6,7%)	5 (10,4%)	12 (23,1%)
IV	4 (3,8%)	3 (6,3%)	7 (4,6%)
Surgical complications	10 (9,6%)	3 (6,3%)	13 (8,6%)
Postoperative mortality	0	1 (2,1%)	1 (0,7%)

Information disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

All procedures performed on patients comply with the ethical standards of institutional and national ethics committees, the 1964 Declaration of Helsinki and its amendments or similar ethical standards.

Informed consent

Informed consent was obtained from each of the patient.

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