Presurgical evaluation of epilepsy patients

Giedrė Gelžinienė, Milda Endzinienė, Nerija Vaičienė, Michel R. Magistris[1], Margaritta Seeck[1]
Department of Neurology, Kaunas University of Medicine, Lithuania
[1]Faculty of Medicine, Geneva University, and Presurgical Epilepsy Unit and Neurology Department, University Hospital of Geneva, Switzerland

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Summary. *Epilepsy surgery has been established as an effective treatment in pharmacoresistant focal epilepsies. Most candidates for epilepsy surgery are patients with partial epilepsy syndromes refractory to medical treatment. The curative surgery procedure is resection of the epileptogenic zone; therefore, precise detection of the site responsible for seizure generation is necessary. Modern structural and functional imaging techniques have made presurgical evaluation less invasive and available for a higher number of patients. Video electroencephalography (EEG) monitoring, high-resolution structural and functional imaging techniques are used widely for presurgical evaluation. When noninvasive evaluation is not sufficient for the detection of the epileptogenic zone, invasive EEG monitoring and intracarotid amobarbital test are used.*

A classical example of a surgically curable epilepsy syndrome is mesial temporal lobe epilepsy with about 70–80% of patients becoming free of seizures after surgery. Results in extratemporal epilepsies are also satisfactory.

Despite worldwide expansion during the recent decade, epilepsy surgery remains underutilized. Better understanding of advances in presurgical evaluation should reduce fears of epilepsy surgery and help to select patients who could achieve complete seizure control or significant amelioration after surgery.

Introduction

Epilepsy is one of the most common chronic neurological diseases, affecting 0.5–1% of the population among which 60% are patients with focal epilepsy (1, 2). Approximately 20% of epilepsy patients become drug-resistant, and more than one-third of them could be candidates for epilepsy surgery (3). Epidemiological study of childhood epilepsy in Lithuania estimated the number of refractory cases as approximately 800, which are possible candidates for presurgical evaluation (4). Introduction of new antiepileptic drugs (AED) has not reduced the percentage of drug-resistant epilepsy significantly. After lack of response to the first AED, the chance to respond to the second AED is around 14% and to the third drug is as low as 5% (5). Epilepsy is considered refractory or pharmacoresistant if seizures continue after 2 years of treatment and/or after treatment with 2–3 appropriately selected drugs in sufficiently high individually tolerated doses with good patient compliance. Patients with refractory epilepsy often use high doses of antiepileptic drugs, usually as polytherapy, and thus are exposed to an increased likelihood of adverse effects (6). Refractory epilepsy patients should be referred to specialized epilepsy centers to evaluate the possibility of surgical treatment, or in more general terms, to understand the nature of their disease. Earlier surgical treatment increases the chance for persistent seizure freedom (7). Moreover, better quality of life after an operation is more likely if patients are operated at younger age (8); therefore, epilepsy surgery should not be delayed. A long course of severe seizures is especially crippling for cognitive and motor development of children. Early surgical treatment could prevent serious brain damage in infants and young children suffering from catastrophic epilepsy of infancy and other severe epilepsy syndromes (9).

The main tasks of presurgical evaluation are patient selection and the identification of the area generating epileptic seizures, but also the verification that this particular cortical area may be removed without severe adverse consequence on neurological and cognitive functions (10). Neurological and neuropsychological testing provides information about cognitive deficits of the seizure-originating site and plays a significant role in determining the risk of adverse cognitive outcome after surgery. During the last decade, multichannel EEG and video monitoring, high-resolution magnetic resonance imaging (MRI), functional MRI, proton emission tomography (PET), single-proton

Correspondence to G. Gelžinienė, Department of Neurology, Kaunas University of Medicine, Eivenių 2, 50009 Kaunas, Lithuania. E-mail: giedregelziniene@hotmail.com

emission computed tomography (SPECT) have become available for presurgical evaluation. It is possible to evaluate most patients with noninvasive methods.

Patients with partial unifocal epilepsies are first-line candidates for epilepsy surgery. Data from Mayo Clinic and Geneva-Lausanne Epilepsy Center showed that 60–70% of patients evaluated for epilepsy surgery finally undergo a neurosurgical procedure (11, 12). About 50% of patients with focal epilepsies have temporal lobe epilepsy, and about 65–85% of these patients become seizure-free after surgery with or without continued AED treatment (13, 14). Positive long-lasting effect on cognition, psychosocial impact (such as driving), employment, family and social status has been noted (15). Unfortunately, epilepsy surgery remains underused. The operative complications are often overestimated: recent studies on morbidity and mortality of operated patients and patients with ongoing seizures found significantly higher morbidity and mortality in the latter group (16).

In Lithuania, the estimated number of patients with active epilepsy is around 20 000, out of these 4000–6000 may be refractory, 1300–2000 may be candidates for presurgical evaluation. Better understanding of the indications and the requirements for presurgical evaluation are of utmost importance.

Concept of the cortical zones implicated in the generation and effects of seizures

Surgery outcome highly depends on the precise definition of the zone responsible for seizure generation. The cortical zone from which the seizures originate is called the *epileptogenic zone* (EZ). This zone has to be distinguished from other suspect areas (17).

The concept of distinct cortical zones may be illustrated with the example of mesial temporal lobe epilepsy (MTLE). The *symptomatogenic zone* is the cortical area activated by the epileptic discharges and responsible for the sensory or behavioral changes (ictal semiology). MTLE seizure may begin with epigastric sensation aura or vomiting, because of the spread to the insula, but it may present also with olfactory hallucinations because of propagation to the orbitofrontal cortex. The *irritative zone* is related to the areas generating the interictal spikes. In case of MTLE, they may be unilateral, but in some patients, interictal spikes may be bilateral although this does not necessarily mean that these patients have bilateral MTLE and are poor candidates. The *seizure onset zone* generates clinical seizures. In case of MTLE, initial rhythmic activity may be recorded in the anterior or inferior medial temporal region, although sometimes the initial ictal activity may be limited to mesial structures, invisible on surface EEG, and only obvious after propagation to lateral temporal structures. The *functional deficit zone* is the brain area relating to deficits observed during the interictal period, e.g. impaired verbal memory in left MTLE. An *epileptogenic lesion* detected by the MRI, as e.g. hippocampal sclerosis in MTLE, may not correspond exactly to the true EZ, which often encompasses also the parahippocampal gyrus or even the temporal neocortex. Moreover, not all brain lesions are epileptogenic and MRI does not detect all epileptogenic lesions, therefore, operation based only on MRI is not appropriate. A precise determination of the above-discussed zones should be performed presurgically in an individual patient to obtain optimal surgical results.

Patient selection for presurgical evaluation

Epilepsy patients should be referred to specialized epilepsy centers if pharmacoresistance becomes evident. Criteria for selection of patients for presurgical evaluation (18):

1. Focal seizure onset should be established.
2. Progressive neurological diseases, such as malignant brain tumor or multiple sclerosis, should be excluded. Malignant tumor may give rise to epileptic seizures, but the operation is performed because of oncological considerations whereas the control of epilepsy is not the primary goal (although it may be a positive "side effect").
3. Resistance to medical treatment with at least two adequate medical regimes at maximal individually tolerated doses, which may exceed the maximal therapeutic dose, should be confirmed. The time period recommended is at least 1–2 years, but it is often shorter in children when pharmacoresistance may become evident already after several months.
4. Seizures should be interfering with daily life activities, social adaptation and be incapacitating for patient.

Mental retardation, low IQ scores or psychiatric diseases are no longer considered as contraindications for epilepsy surgery (19).

Stages of presurgical evaluation

Patients with refractory epilepsy who meet the criteria should undergo further presurgical evaluation. The latter is divided into a noninvasive and invasive phase (Table). For the large majority of patients, noninvasive phase evaluation suffices to determine if epilepsy surgery can be performed. If the epileptogenic focus and/or adjacent vital cortex are not precisely determined after noninvasive evaluation, an invasive phase is necessary.

Table. **Phases of presurgical evaluation of epilepsy**

Phase	Evaluation methods
Phase I – noninvasive methods (sufficient in up to 90% of patients)	• Video monitoring and surface EEG (and sphenoidal recording if possible) >30 channels; • MRI and fMRI • PET and SPECT • Neuropsychological evaluation • Wada test
Phase II – invasive methods	• Intracranial EEG recording by using: – subdural electrodes – depth electrodes – foramen ovale electrodes

EEG – electroencephalography; fMRI – functional magnetic resonance imaging; MRI – magnetic resonance imaging; PET – proton emission tomography; SPECT – single-proton emission computed tomography.

A. Noninvasive evaluation methods (phase I)

Procedures and methods of noninvasive phase include detailed history of seizure semiology and frequency, previous medication treatments, complete physical and neurological evaluation. Neuropsychological testing and psychiatric evaluation should complement the necessary work-up.

EEG

Prolonged surface (scalp) EEG recordings are essential for the diagnosis of epilepsy. Compared to everyday practice, the localization of epileptiform activity should be identified more precisely in presurgical evaluation. Therefore, additional electrodes are usually necessary. The most common additional electrodes are anterior temporal electrodes and electrodes between or below the standard 10–20 electrodes placement (20). Sphenoidal electrodes are often used when mesial temporal lobe epilepsy is suspected. Standard setups of multichannel electrodes are now available, and the most modern machines include simultaneous video recording. Usually several wake-sleep EEGs and recordings of 4–10 seizures are required to verify a unifocal onset. Cautious tapering of the antiepileptic drugs may be used to increase possibility of seizure occurrence and registration.

Sophisticated EEG techniques allow combining EEG data with brain imaging to better define the epileptogenic zone (21). Studies showed that 128-channel EEG source imaging might localize the epileptogenic area correctly in 94% of patients and allow resection of maximal source in almost 80% of patients (22). Further studies will show if these sophisticated surface recordings reduce the need for intracranial recordings.

Magnetic resonance imaging (MRI)

MRI is the imaging method of choice for the detection of an epileptogenic lesion by providing anatomical details of brain lesions (23). MRI techniques are improving; therefore, patients who were considered "MRI negative" may reveal structural changes with advanced MRI machines. High-resolution MRI techniques are used in presurgical evaluation because important anomalies may not be detected with standard MRI (21).

Protocols for MRI in presurgical evaluation should include: 1) T1-weighted volumetric data set acquired in an oblique coronal orientation, orthogonal to the axis of hippocampus in 0.9–1 mm slices; 2) oblique coronal spin echo sequences and heavily T2-weighted sequences perpendicular to the hippocampus; 3) fluid attenuation inversion recovery (FLAIR) sequences in coronal and axial axes are recommended (24).

Since the most common cause of localization-related epilepsy is mesial temporal sclerosis, high attention is paid to the evaluation of hippocampus on MRI (Fig.). Experience and several studies indicate that in most cases invasive EEG is not needed if MRI detects hippocampal sclerosis in patients with MTLE and video-EEG, neuropsychology and other brain imaging data (if available) are concordant (25).

Epileptogenic tumors and cortical migration disorders constitute other pathological findings detected in epilepsy patients; rare structural lesions include Sturge-Weber syndrome, porencephalic cysts, scars, and other pathology. In about 20% of patients, no structural abnormality may be found (26). It is worth mentioning that about 15% of epilepsy patients may have dual pathology (27), and a recent study indicates that this value may be even higher (28). These obser-

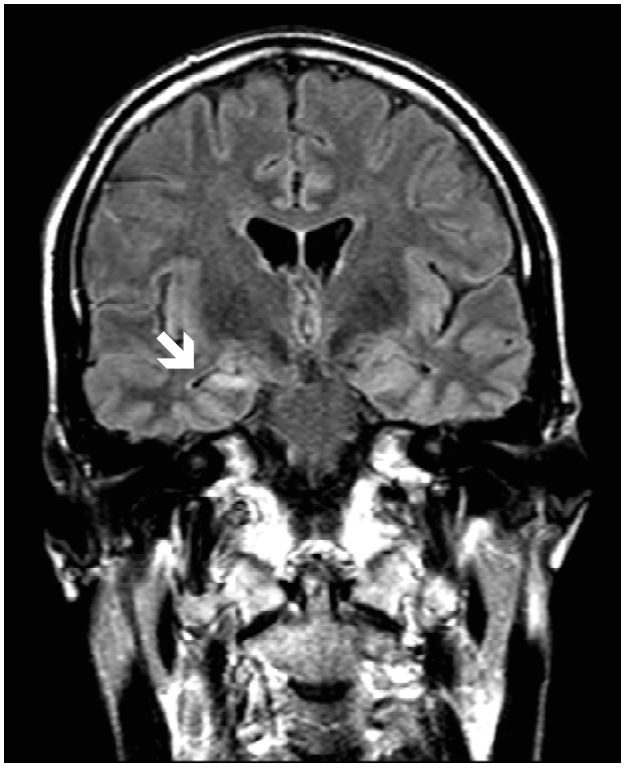

Fig. **Magnetic resonance imaging (FLAIR sequence) of a patient with right hippocampus sclerosis**

FLAIR – fluid attenuation inversion recovery.

vations underline the need for comprehensive presurgical evaluation not relying solely on MRI.

Functional MRI techniques

Diffusion weighted imaging (DWI) and more recent diffusion tensor imaging (DTI) are based on sensitivity of displacement of water molecules and allow visualizing cellular and microstructural disorganization that may not be visible on MRI (29). In some cases, DTI may detect neuronal loss or gliosis caused by chronic seizures, or subtle abnormalities caused by head trauma that do not directly relate to the source of the seizures (30). Further studies will determine the usefulness of DTI to localize epileptic foci.

Functional magnetic resonance imaging (fMRI) is based on blood oxygen level-contrast, reflecting discrete changes in deoxyhemoglobin presumably relating to neuronal activation (29). The combination of fMRI and EEG recorded inside the magnet may represent another tool to identify the neuronal activity related to epileptogenic discharges; however, this method requires optimal patient collaboration to minimize movements and frequent discharges (otherwise long fMRI acquisitions are required) (31). This method is safe and precise in localizing discrete epileptic foci, particularly in patients with extratemporal epilepsy (32), if enough discharges occur while the patient is inside the magnet.

In the context of presurgical epilepsy evaluation, another clinical application of fMRI has become widely used. The preoperative determination of cortex areas associated with specific brain functions such as sensory, motor, language and, more recently, also of memory functions is carried out with fMRI. Albeit the paradigms to identify areas related to language and memory are still under investigation, and fMRI alone may not yet suffice to plan the extent of surgical resection (23), motor and sensory fMRI have become an integrated part of presurgical preparation.

Magnetic resonance spectroscopy (MRS) evaluates changes of cerebral metabolites, such as N-acetyl-aspartate, creatinine or lactate, and neurotransmitters, such as GABA, glutamate, or glutamine (23). The main principle of the method relies on the different spectral frequencies of nuclei according to their compounds. N-acetyl-aspartate concentrations are highest in neurons, and its reduction indicates neuronal loss or transient dysfunction in epileptogenic area or both (32, 33).

Functional imaging with PET and SPECT

PET and SPECT are used and studied since the 1980s and in some centers are parts of the "routine" work-up of patients with chronic epilepsy. These methods allow detecting relative focal hypo- or hyperactivity of the epileptogenic area, depending on the moment of injection. This is the reason why simultaneous monitoring of EEG when injecting the tracer should be carried out routinely. These techniques are especially useful in patients with negative MRI. Interictal PET has an established role in epilepsy evaluation showing regional hypometabolism in the involved area (34, 35). Focal ictal onset in surface and sphenoidal EEG together with focal interictal PET hypometabolism zone in the temporal lobe speaks strongly in favor of anterior temporal lobe epilepsy, and further invasive EEG recording is usually not needed (36). PET became a useful tool in the evaluation of children with intractable epilepsy syndromes, such as infantile spasms or tuberous sclerosis (37).

SPECT is more widely available than PET because of lower costs. SPECT exams reflect the momentary perfusion (i.e. if injected during a seizure, it presumably reflects the focal hyperperfusion of the active focus) (38). Ictal SPECT provides localizing information, in particular if compared with the interictal

exam. Interictal SPECT alone provides very poor localizing information and should no longer be performed (39). Both ictal and interictal SPECT can be analyzed by subtraction algorithms and co-registered with MRI (SISCOM). This technology improves the yield over visual analysis, given that subtle changes become more conspicuous (40).

Data of a recent study show that preoperative PET examination localizes dysplastic lesions and extratemporal epilepsy better, whereas SPECT is superior to PET in patients with temporal lobe epilepsy and/or tumors (41).

Neuropsychological evaluation

Neuropsychological evaluation is an important part of presurgical evaluation that helps to localize the functional deficit zone and predict postoperative cognitive outcome (17). This requires a battery of tests, in the language spoken and read in a given country, targeting the cognitive profile of each hemisphere and lobe (i.e. not simply an IQ test). Wechsler Memory Scale (WMS) is one of the most widely used batteries (42). Among the domains memory and language functions are most frequently studied using various tests such as Rey-Osterrieth Figure, 15 Words and 15 Signs tests, Boston Naming Test, Verbal and Semantic fluency tests.

Memory deficits are frequent in patients with temporal lobe epilepsy and to a lesser extent in some patients with extratemporal lobe epilepsy. While left temporal dysfunction is most often associated with verbal memory deficits, right temporal dysfunction is rather associated with nonverbal memory impairment. Therefore, testing addresses verbal and nonverbal tasks separately (43). Intact verbal memory is mandatory in most professions; therefore, presurgical neuropsychological evaluation has to determine the risk of significant postoperative impairment of verbal memory by specialized psychologist or doctors.

Intracarotid amobarbital procedure (IAP; "Wada test")

Intracarotid amobarbital procedure (IAP) was introduced by Dr. Jun Wada to assess hemispheric language dominance (44), and it was modified by Milner et al. to test also memory function and predict possible postoperative amnesia (in 45). The principle of the intracarotid amobarbital procedure (IAP) is to provoke a transitory anesthetization of one hemisphere by injecting amobarbital sodium into the carotid artery. The remaining functions of contralateral hemisphere are examined using neurological and neuropsychological tests (46). While there is no uniform protocol, most centers determine motor functions (to verify sufficient anesthesia), visual field, speech production and comprehension, the presence of neglect, verbal and visuo-verbal memory performance. The anesthetizing effect is short (around 10 minutes), so the development of a strict, timely protocol covering all major cognitive aspects to be tested is mandatory. The procedure is often repeated with the contralateral carotid artery in order to determine possible dissociations of language functions or visuo-spatial phenomena (47). Selective IAP has been developed targeting in particular the hippocampus through selective catheterization of the anterior choroidal artery or posterior cerebral artery (48), without the risk of a concomitant aphasia hampering proper memory evaluation.

Major memory deficits observed after anesthetization of region of intended resection require careful consideration of the surgical indication because remaining structures on the contralateral hemisphere may not compensate for the removed tissue and cause unacceptable deficits after surgery (49, 50). Functional MRI may become an alternative to invasive IAP that always requires a full angiography. Lateralization (albeit not localization) of language cortex is today relatively reliably performed with fMRI (51), in particular if a test battery is used and just one single paradigm.

The indication for the Wada test, a rather invasive procedure, depends on the center. In the Geneva-Lausanne program, only selected patients undergo this exam, while in other centers it is part of the routine or offered to all patient before an intervention in the possibly language dominant hemisphere. Noninvasive evaluation was sufficient in 85% of patients with temporal and extratemporal lobe epilepsy evaluated in the Geneva-Lausanne presurgical epilepsy unit (52).

B. Invasive evaluation phase (II)

Invasive EEG recording

Invasive EEG recording is recommended, according to European Standards for presurgical evaluation, when: 1) noninvasive investigation data are discordant; 2) the degree of precision required for a tailored surgical approach cannot be obtained by noninvasive evaluation (53). The type of intracranial electrodes and recording depends on the questions to be solved. There are several sorts of invasive electrodes: depth electrodes, subdural strip and grid electrodes, foramen ovale electrodes. If electrodes are made from stainless material, they are MRI compatible. If non-MRI compatible electrodes are chosen, then electrode positions need to be determined by CT scan. Co-registration

with the patient's MRI provides an equally good localizing precision, but lower costs. Subdural grid electrodes are most suitable to identify "eloquent cortex" and to differentiate these zones from the epileptic focus. Since grids require rather large craniotomies, only unilateral exploration is performed. Subdural strips are often used, when less crucial areas are investigated (together with grids or depth electrodes), and can be inserted bilaterally. In contrast to subdural electrodes, depth electrodes are implanted intracerebrally and require a stereotactic frame set-up. Their advantage is that they require small craniotomies and may usually be performed under local anesthesia (less costly). Depth electrodes contain up to 20 evenly spaced contacts. The EEG signal quality is usually better than that for subdural electrodes, and they allow excellent recordings from deep structures (and inside closed structures such as the amygdale), which are more difficult with subdural contacts. They can be inserted bilaterally and into several lobes, either perpendicular to the lateral skull or orthogonal from the occipital lobe, e.g. if recording from the entire (or almost entire) hippocampus is warranted. Removal of depth electrodes is easier compared to subdural electrodes. The procedure may be performed at bedside without local or general anesthesia. However, the main disadvantage is the limited coverage of the lateral cortical surface making cortical mapping difficult.

Foramen ovale electrodes are less frequently used. It is often referred to as "semi-invasive", but it is also inserted into the skull, i.e. the term "semi-invasive" does not appear to appropriate. Foramen ovale electrodes record only from mesial temporal structures (in particular the hippocampus), and the indication "par excellence" is the determination of left or right mesial temporal onset (i.e. mesial onset is suspected, but the side or side predominance is not known).

Invasive EEG recording comports risks as any invasive procedure. The overall reported complication rate of subdural electrodes (with grids) is up to 14% with permanent sequels in about 2% of patients (54). Most frequently, infection or bleeding is encountered. Intracerebral hemorrhage is rare (about 1%) (55). The most frequent side effect of foramen ovale electrode placement is pain related to trigeminal irritation, mostly transient (54). Invasive EEG monitoring should not exceed two weeks (55).

Invasive electrodes record epileptiform activity only from a restricted area, adjacent to the contact. The epileptogenic focus may be incorrectly localized if ictal activity starts in structures that are not "covered" by the electrodes (57). The problem of "spatial undersampling" is well known and can be minimized with an excellent phase I investigation, regarding all hypotheses of seizure origin(s) in an individual patient. Spatial undersampling is suspected if the ictal EEG onset does not precede the clinical onset. This situation is related to a less favorable surgical outcome (58).

Recommendations for epilepsy center

The success of surgical treatment is highly dependent on the experience and the number of patients evaluated and operated each year in a given epilepsy center. Possible gold standards of operated patients (20 patients a year or 50 operations in 4 years) have been published (18). ILAE Commission on Neurosurgery of Epilepsy suggested possible settlement of "basic centers" in places where resources are limited and "reference centers", which are able to perform the full range of established presurgical evaluation and surgical treatment (53).

Commission on European Affairs of the International League Against Epilepsy in recognition of the fact that epilepsy surgery in the Central and Eastern European countries is underdeveloped in 2007 has initiated a new format of educational courses and fellowships targeted mainly to this region.

Conclusion

Surgery is the treatment of choice in selected patients with refractory epilepsy, in particular those with hippocampal sclerosis. A comprehensive presurgical evaluation in a specialized center is a prerequisite before offering this therapy, since ictal recording remains the mainstay of the presurgical diagnosis. Eligibility of a candidate to surgery should not be based on MRI alone or interictal EEG alone. MRI-negative focal epilepsy may have as good an outcome as MRI-positive focal epilepsy, provided that a thorough evaluation was done.

In contrast to the still omnipresent assumption that surgery is the last resort, it should be considered as the second or third option, if two or three drugs failed, and if the patient is young. Thus, across the whole patient's life, persistent seizures are more dangerous than the operation, and this finding should conduct any suggestion for or against the surgical intervention. Even if evaluation does not lead to surgery, it may result in a better epilepsy syndrome diagnosis and possible treatment optimization.

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Sergančiųjų vaistams atsparia epilepsija atranka chirurginiam gydymui

Giedrė Gelžinienė, Milda Endzinienė, Nerija Vaičienė, Michel R. Magistris[1], Margaritta Seeck[1]
Kauno medicinos universiteto Neurologijos klinika, Lietuva, [1]Ženevos universiteto Medicinos fakultetas ir Ženevos universiteto ligoninės Priešchirurginės epilepsijos skyrius ir Neurologijos klinika, Šveicarija

Raktažodžiai: vaistams atspari epilepsija, epileptogeninė sritis, epilepsijos chirurgija.

Santrauka. Chirurginis gydymas gali būti veiksmingas metodas gydant sergančiuosius vaistams atsparia židinine epilepsijos forma. Planuojant chirurginį gydymą, svarbu tiksliai nustatyti, kurioje galvos smegenų žievės srityje generuojami epilepsijos priepuoliai. Šiuolaikiniai struktūriniai ir funkciniai vaizdiniai tyrimai, pvz., vaizdo elektroencefalografijos (EEG) stebėsena, didelės skiriamosios gebos struktūriniai bei funkciniai vaizdiniai tyrimai sumažino invazinių tyrimų poreikį, todėl ikichirurginį ištyrimą galima atlikti didesniam ligonių skaičiui. Jei neinvaziniais tyrimais epileptogeninės srities nustatyti nepavyksta, tyrimas tęsiamas atliekant invazines procedūras – invazinės EEG stebėseną bei intrakarotidinį amorbitalio testą.

Chirurginiu būdu pagydomo epilepsinio sindromo pavyzdys yra vidinės temporalinės skilties dalies (angl. *mesial temporal lobe epilepsy*) epilepsija. Apie 70–80 proc. šia epilepsijos forma sergančiųjų po operacijos nepatiria priepuolių. Kitos lokalizacijos epilepsijos chirurginio gydymo rezultatai taip pat pakankamai geri.

Pasaulyje chirurginis epilepsijos gydymas taikomas vis plačiau, tačiau dar nepakankamai. Geresnis ikichirurginio epilepsijos ištyrimo galimybių supratimas turėtų sumažinti nepagrįstą operacijos baimę ir padėti tinkamai atrinkti ligonius sėkmingam chirurginiam gydymui.

Adresas susirašinėti: G. Gelžinienė, KMU Neurologijos klinika, Eivenių 2, 50009 Kaunas
El. paštas: giedregelziniene@hotmail.com

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