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Selecting Patients for Epilepsy Surgery

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Abstract About one third of patients with focal epilepsy experience seizures despite adequate medical treatment. In this population, successful epilepsy surgery improves life expectancy and health-related quality of life, while reducing health care costs as a result of reduced hospital admissions, emergency department visits, and use of antiepileptic drugs. The effectiveness of epilepsy surgery and low incidence of surgical complications have been established by numerous studies over several decades. The International League Against Epilepsy recently issued a definition of drug-resistant epilepsy for early identification of patients who are unlikely to be treated successfully with medical therapy alone. Potential surgical candidates are identified through a detailed seizure and medical history, physical examination, and the use of video electroencephalography and neuroimaging. A presurgical evaluation should be considered as soon as drug resistance becomes evident.

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Introduction

Epilepsy is the second most common chronic neurologic disorder, affecting more than 50 million people worldwide, with 2 million new cases each year [1]. The prevalence of epilepsy is 8.0 per 1,000 in the United States [2] and may be twice as high in developing countries. Although most patients can be treated successfully with antiepileptic drugs (AEDs), an estimated 30% to 40% of people with epilepsy are drug resistant [3••]. Thus, in the United States, the number of patients with drug-resistant epilepsy (DRE)—approximately 700,000—is higher than the number of those affected by Parkinson's disease (349,000) and multiple sclerosis (266,000) combined [2]. These patients are burdened with the highest degree of morbidity and disability and are responsible for most of the economic impact of epilepsy. The mortality of people with DRE is increased fourfold to sevenfold compared with the general population. Epilepsy surgery increases survival by up to 5 years and increases quality-adjusted life expectancy by 7.5 years [4••]. Yet, epilepsy surgery is markedly underutilized. In fact, over the past 15 years, the mean duration of epilepsy before referral for surgical consideration in patients who ultimately underwent temporal lobectomy exceeded 20 years [5••]. This may be explained partly by repeated periods of remission and relapse in some patients who ultimately elect to have

surgery [6]. However, the primary reason for underutilization of epilepsy surgery relates to the failure of health care providers to recognize DRE, the lack of standardization of a definition of drug resistance, and limited awareness of the effectiveness of epilepsy surgery and the relatively low rate of surgical complications [7••]. In this review, we discuss the criteria for DRE, the identification of surgical candidates using presurgical evaluation, and the differentiation of epileptic seizures from non-epileptic paroxysmal events (NPEs).

Recognizing Drug-Resistant Epilepsy

A commission of the International League Against Epilepsy recently defined DRE as "a failure of adequate trials of two tolerated, appropriately chosen and used AED schedules whether as monotherapy or in combination to achieve sustained seizure freedom" [8••]. Multiple studies in the past decade have shown that the chances of sustained seizure freedom decrease progressively with each failed AED. In a population of patients with newly diagnosed epilepsy at a tertiary center, the rates of seizure freedom for at least 1 year were 50.4%, 10.7%, and 2.7% during treatment with the first, second, and third treatment schedules, respectively [8••]. Others have reported a 15% chance of obtaining seizure freedom for at least 1 year after treatment changes in patients with poorly controlled symptomatic and cryptogenic epilepsy [9]. However, 25% of those who become seizure-free for 1 year ultimately relapse [10]. In a study of children with epilepsy, 57% of patients who had not responded favorably to the first two AEDs subsequently achieved periods of remission of at least 1 year [11•]. However, relapses occurred in 68% of cases, and repeated remissions and relapses were common. Thus, an unfavorable response to two AED trials may be evident as early as 6 months after the onset of epilepsy. Clinical factors associated with subsequent DRE include an early age of onset, more than one seizure per month, remote symptomatic etiology, abnormal neurodevelopmental status, a greater number of failed drugs, and longer epilepsy duration [6, 12]. Electroencephalography (EEG) features predictive of DRE include multiple epileptic foci [13] and frequent spikes in patients with temporal lobe epilepsy (TLE) [14]. TLE carries a higher risk of DRE compared with extratemporal epilepsies (ExTLEs) [15]. The presence of a structural abnormality on MRI, such as neoplasms, vascular malformations, malformations of cortical development, encephalomalacia, hemorrhage, and most importantly, hippocampal sclerosis (HS), is a major predictor of drug resistance in both children and adults with epilepsy [16]. These epileptogenic lesions may escape detection on routine imaging studies. Thus, the neuroimaging of patients with DRE must be tailored to the electroclinical diagnosis.

Using the Presurgical Evaluation to Select Epilepsy Surgery Candidates

General Concepts

A presurgical evaluation should be considered in all patients with features of focal epilepsy who meet the aforementioned definition of DRE. The goal of the evaluation is to delineate the *epileptogenic zone* (EZ). This is the area of cortex essential for the generation of seizures whose complete resection or disconnection renders the patient seizure-free. With current technology, the EZ cannot be visualized directly. However, it can be estimated by a combination of five other cortical zones defined in the presurgical evaluation [17]:

- The *symptomatogenic zone* is responsible for the initial symptoms of an aura or a seizure, thus it can be defined using history and video recordings of seizures.
- The *functional deficit zone* corresponds to interictal neurologic or neuropsychological deficits that may be detected through the neurologic examination, neuropsychological testing, or functional imaging.
- The *irritative zone* generates interictal epileptiform discharges; it is estimated through interictal EEG.
- The *ictal onset zone* creates the initial seizure discharges; it can be approximated through ictal EEG recordings and ictal single photon emission CT (SPECT).
- An *epileptogenic lesion* is a structural imaging abnormality responsible for the generation of seizures; it may be visualized by MRI.

The putative EZ may be closely related to *eloquent cortical areas*. These may be defined using neuropsychological testing, functional MRI, Wada testing, and invasive EEG with electrocortical stimulation. However, most of the cortex is noneloquent, and the EZ frequently resides in silent areas.

Clinical History and Seizure Symptomatology

Some of the predictors of DRE are actually associated with a favorable outcome after epilepsy surgery. These include early age at onset, TLE, and the presence of an epileptogenic MRI lesion [18, 19]. On the other hand, there is no single feature in the history that automatically precludes epilepsy surgery. In particular, a lifelong history of seizures, older age, diffuse symptomatic etiology such as meningitis, developmental delay, and focal neurologic deficits do not exclude a surgical approach when the results of the presurgical evaluation delineate an EZ that can be resected without substantial neurologic or psychological impairment.

Many signs and symptoms observed during the ictal and postictal periods provide lateralizing and localizing value that can help identify the hemisphere or lobe of seizure origin. Common signs and symptoms with localizing or lateralizing value are listed in Table 1 [20, 21]. Localizing symptoms at the beginning of a seizure indicate a restricted symptomatogenic zone. Although the patient's and bystanders' ability to provide a detailed seizure history may depend on their age, intellect, mental status, and mood, this information may provide essential information about the area of seizure origin.

An epileptic aura reflects an early and restricted activation of a symptomatogenic area. It may represent the electrical seizure onset or the earliest spread of the electrical seizure activity from a silent area to symptomatogenic cortical areas. A typical example of this concept is the abdominal aura, commonly seen in patients with TLE due to HS. In this case, the electrical seizure activity originates in the sclerotic hippocampus; however, the rising abdominal sensation is caused by activation of the anterior insular cortex [22].

Somatosensory auras reflect epileptic activation of the contralateral primary somatosensory area (S1) in the postcentral gyrus, secondary somatosensory area (S2) in the superior bank of the sylvian fissure, or insula (the latter two with bilateral representation). These areas have a somatotopic organization, and their activation may produce paresthesias, pain, or thermal sensations. A well-localized somatosensory aura usually indicates an EZ in the perirolandic area [23]. Sensory phenomena with an ill-defined or predominantly proximal or bilateral distribution suggest ictal activation of the S2 area or supplementary sensorimotor area.

Simple visual auras (amaurosis or hallucinations of static, moving, or flashing lights, shapes, or colors) localize to the primary visual cortex of the mesial occipital lobe. This also is organized in a somatotopic fashion with inferior parts of the visual field represented above the calcarine fissure, and vice versa. Visual association areas are involved in the perception of color and movements as well as complex visual phenomena, such as distortions and changes in dimensions. When visual phenomena are lateralized, they always point to the contralateral hemisphere [24].

Elementary auditory phenomena can be evoked by electrocortical stimulation of Heschl's transverse gyrus. Complex auditory hallucinations point to the auditory association areas in the superior temporal gyrus. Each hemisphere receives input from both ears, with a stronger representation of the contralateral side [21]. The symptomatogenic zone for epileptic vertigo is close to the visual and auditory association cortices at the temporoparietal junction. Vertiginous auras are observed more frequently in right hemispheric epilepsies [25].

Olfactory auras often are associated with other forms of auras. The symptomatogenic zone includes the amygdala, olfactory bulb, and insula. Gustatory auras point to the parietal operculum or the anteromesial basal temporal cortex. Neither has lateralizing value [21].

Psychic auras include strong emotional experiences (anxiety, fear, rarely elation), distortions of familiarity (déjà vu, jamais vu), and revocations of complex memories. Fear localizes to the amygdala or anterior hippocampus, whereas pleasant sensations, déjà or jamais vu, and complex memories indicate involvement of more distributed cortical networks involving the mesial basal and lateral temporal neocortical areas. They do not have clear lateralizing value [21].

Motor signs that provide a lateralizing value over 80% of the time are head and/or eye version, unilateral dystonic arm posturing, unilateral clonic or tonic activity, the "figure 4 sign" (extension of one arm with flexion of the opposite arm at the elbow), and postictal palsy, all suggesting a seizure focus in the contralateral hemisphere [20]. Unilateral ictal eye blinking and postictal nose wiping localize to the ipsilateral hemisphere (usually temporal lobe), with a specificity of 83% and 92%. Ictal spitting or vomiting and ictal speech (comprehensible speech during a seizure with impaired awareness) suggest seizure onset in the nondominant temporal lobe, with a specificity of 75% and 83%, respectively. Automatisms with preserved consciousness indicate seizure origin in the nondominant hemisphere, usually the temporal lobe, whereas ictal aphasia or dysphasia (inability to communicate while awareness is preserved) points to the dominant hemisphere, with 100% specificity. The value of any single sign must be interpreted in the context of the ictal sequence because too much emphasis on a single feature may be misleading. Head versive, focal tonic, and clonic activity; unilateral dystonic arm posturing; the figure 4 sign; postictal nose wiping; and unilateral postictal paresis have been observed rarely in patients with generalized epilepsy [26].

Mesial TLE due to HS (MTLE-HS) is the prototype of surgically remediable epilepsy in adolescents and adults [27]. There are genetic predispositions to MTLE-HS, such as generalized epilepsy with febrile seizure plus (GEFS+) and familial MTLE, in which a genetic defect causes MTLE. Frequently, an initial precipitating incident is present, such as complex febrile seizures, trauma, hypoxia, or intracranial infection, usually before the age of 5 years. Classically, there is a latent period between the initial precipitating incident and the onset of habitual seizures in the second or third decade of life. The habitual seizures initially may respond to AEDs; however, DRE ultimately is

Table 1 Seizure symptomatology with localizing or lateralizing value

Domain	Clinical feature	Description	Localization[a]	Lateralization
Sensory	Somatosensory aura	Unilateral, localized tingling, numbness, electrical shock-like sensation, heat, pain, sense of movement, or desire to move	Primary sensory cortex, secondary somatosensory areas	CL (if unilateral)
	Simple visual aura	Flashing or flickering lights, spots, simple patterns, scotoma, or amaurosis	Primary visual cortex	CL
	Complex visual aura	Visual distortions, changes in dimension	Visual association cortex	CL (if unilateral)
	Auditory aura	Buzzing, drumming sounds, single tones, or more complex auditory hallucinations, including melodies	Primary and secondary auditory cortex	CL (if unilateral)
	Olfactory aura	Burning, rotten, unnatural unpleasant smells	Amygdala, insula	NonLAT
	Gustatory aura	Metallic or rubbery, unnatural, unpleasant sensations	Parietal operculum, basal temporal cortex	NonLAT
	Abdominal aura	Nausea, emptiness, tightness, "butterflies," rising abdominal sensation	Insula	NonLAT
Psychic	Fear	–	Amygdala, hippocampus, mesial frontal	NonLAT
	Distortions of familiarity	Déjà vu: sensation of being familiar with a new situation Jamais vu: sensation that a familiar context appears new	Mesial temporal, temporal association cortex, rhinal cortex	NonLAT
	Multisensorial hallucinations	Revocation of complex memories	Mesiobasal limbic cortex, neocortical temporal, temporoparieto-occipital junction	NonLAT
Autonomic	Autonomic alterations	Hot flashes, hypersecretion, piloerection, sweating, vomiting	Mesial temporal, insular, anterior cingulum, orbitofrontal	NonLAT
Motor	Focal clonic activity	Unilateral, localized, rhythmic repetitive movements	Primary and secondary motor cortex	CL
	Focal tonic activity	Unilateral, localized, sustained muscle contraction	Supplementary motor area, secondary motor cortex, anterior cingulum	CL
	Versive head/eyes	Sustained, forced conjugate ocular, cephalic, and/or truncal rotation or lateral deviation	Secondary motor cortex, frontal eye fields	CL
	Unilateral dystonic arm posturing	Sustained contractions of agonist/antagonist muscles, resulting in pronation and extension of the forearm, flexion of wrist, extension of digits	Activation of basal ganglia	CL
	Figure of 4 sign	Asymmetric contraction of upper limbs resembling a figure 4 with arm extension contralateral to focus, ipsilateral arm flexed at elbow, occurring during initial phase of GTC	Supplementary motor area, precentral areas	CL
	Automatisms with preserved responsiveness	Coordinated, repetitive, motor activity without impaired awareness	Temporal lobe, rarely mesial frontal	ND
	Postictal paresis	Postictal weakness involving arm, face, or leg	Exhaustion of primary or secondary motor cortex	CL
	Asymmetric termination of the clonic phase	Unilateral persistence of clonic jerks at the end of GTC	Exhaustion of hemisphere of seizure onset	IPSI
Language	Ictal/postictal aphasia	Inability to speak or comprehend with preserved consciousness	Anterior and posterior language areas	D
	Ictal speech	Ability to speak with impaired awareness	Temporal	ND

[a] Typical localizations are provided.

CL contralateral; *D* dominant; *GTC* generalized tonic-clonic seizure; *IPSI* ipsilateral; *ND* nondominant; *NonLAT* nonlateralizing.

(*Modified from* Loddenkemper and Kotagal [20] and Rona [21].)

observed in most patients. Typical symptomatology of seizures includes an abdominal or psychic aura followed by impaired awareness with oral/manual automatisms. Frequently observed lateralizing signs are unilateral hand automatisms associated with contralateral arm dystonia, ictal speech (nondominant temporal), postictal aphasia (dominant temporal), and postictal hemiparesis. Some manifestations can distinguish mesial from neocortical temporal lobe epilepsy (NTLE). A history of febrile convulsions, abdominal aura, and unilateral dystonic arm posturing are more common in MTLE, whereas nonspecific auras and early clonic activity without automatisms are more frequent in NTLE [27]. Most patients with MTLE-HS have concordant ictal and interictal EEG lateralization and ipsilateral hippocampal atrophy on MRI. MTLE can be diagnosed on electroclinical findings with an accuracy of about 75% [27].

Extratemporal lobe epilepsy represents a heterogeneous group of disorders with variable clinical manifestations and response to therapy. Surgical outcome in ExTLE is inferior to that of TLE, and invasive monitoring is more often necessary to delineate the EZ. Frontal lobe epilepsy (FLE), the most common type of ExTLE in adults and children, is classified by the compartment of seizure origin [28]. Epilepsy of the supplementary motor area is characterized by seizures with sudden asymmetric tonic posturing (fencing posture), vocalization, and preserved awareness. Perirolandic epilepsy presents with focal motor or sensory seizures of the contralateral face, arm, or leg with or without a jacksonian March (spread of the ictal manifestations from one part of the body according to the homunculus pattern of cortical representation). Seizures of orbitofrontal lobe epilepsy feature an olfactory aura, autonomic signs, staring, unresponsiveness, automatisms, motor agitation, and contralateral version, often mimicking TLE. Dorsolateral FLE produces seizures characterized by unilateral tonic and/or clonic activity, contralateral version of the head and/or eyes, arrest of activity and speech, and unresponsiveness if the frontopolar region is involved. Cingulate seizures involve unresponsiveness, automatisms, autonomic changes, affective manifestations (aggression, screaming, and fear), and rarely ictal laughing or crying. Opercular epilepsy presents with orolaryngeal disturbances (swallowing, salivation, mastication) and speech arrest, followed by motor involvement of the contralateral face and upper extremity. No single historical or semiologic feature reliably distinguishes seizures of frontal from those of temporal origin. However, the constituents of an ictal sequence may assist in the differentiation of seizures from these areas (Table 2) [29].

Seizures arising from the parietal, occipital, and insular lobes are most apt to be mislocalized or mislateralized because of their tendency to propagate rapidly to the temporal or frontal regions [30, 31]. Parietal lobe epilepsy is characterized by seizures with contralateral somatosensory aura and ipsilateral head or eye turning, followed by asymmetric tonic posturing, contralateral version, unilateral clonic activity, or automatisms [32]. Occipital lobe epilepsy often presents with elementary visual auras (nonformed visual phenomena such as stars, flashes, or bright spots), visual field defects, forced blinking, and eye movement sensations, followed by unresponsiveness and automatisms, reflecting spread to temporal areas, or asymmetric tonic posturing and unilateral clonic activity, indicating propagation to frontal areas [33]. Pure insular epilepsy typically presents with laryngeal discomfort, retrosternal or abdominal heaviness, perioral and contralateral hemibody somatosensory symptoms, and dysphonic or dysarthric speech, followed by tonic activity of the contralateral face and arm [31]. However, seizures arising from the insula often spread rapidly to adjacent areas, mimicking TLE or other focal epilepsies, or begin simultaneously in temporal, frontal, or parietal structures, leading to difficulty in localizing the EZ.

Focal seizures must be differentiated from NPEs that comprise a spectrum of motor, sensory, and behavioral paroxysms not due to epileptic activity, but mimicking epilepsy nonetheless. Epileptic and nonepileptic events may coexist in a given patient, underscoring the importance of early recognition and appropriate treatment before epilepsy surgery is considered. NPEs may be caused by syncope, metabolic derangements (hyper- or hypoglycemia), sleep-related paroxysmal phenomena, and neurologic conditions such as migraine, movement disorders, and transient ischemic attacks. However, in practice, psychogenic nonepileptic seizures (PNES) represent the most common form of NPE. Clinical history obtained from both the patient and observers is useful in distinguishing epileptic seizures from PNES, although video-EEG (VEEG) is the only way to definitively differentiate the two. Reproducible precipitants of events, including sleep deprivation, alcohol, or menses, suggest the diagnosis of epilepsy. Oral lacerations including tongue biting, urinary incontinence, event-related significant injury, and myalgias are experienced more often by patients with epilepsy. Occurrence of the events only in the presence of observers and events triggered by emotional stress raise suspicion of PNES. Historical features such as chronic pain or fatigue, fibromyalgia, and somatization disorder, as well as histrionic personality features, have a high predictive value for the diagnosis of PNES. Gradual onset and termination, irregular discontinuous asynchronous motor activity, waxing and waning intensity, side-to-side head movements, pelvic thrusting, opisthotonic posturing, and preserved awareness during bilateral motor activity are characteristic features of PNES [34]. With rare exceptions, the absence of an electrographic seizure pattern on EEG at the time of the recorded event confirms the

Table 2 Seizure symptomatology in temporal versus frontal lobe epilepsy

Feature	Frontal lobe epilepsy	Temporal lobe epilepsy
Onset and offset	Sudden	Gradual
Duration	Brief (<1 min)	Longer (>1 min)
Occurrence	Often sleep related	Usually when awake
Seizure clusters	Common	Uncommon
Aura type	Olfactory, gustatory, cephalic	Epigastric, psychic, auditory
Time to motor component	Early, prominent	Later in ictal sequence
Automatisms	Uncommon	Common
Autonomic signs	Uncommon unless onset in orbitofrontal or cingulum	Common
Vocalization	Common	Uncommon
Unilateral clonic activity	Common	Uncommon
Unilateral dystonic arm posturing	Uncommon	Common
Asymmetric tonic posturing	Common	Uncommon
Versive head/eyes	Common	Uncommon
Violent motor behaviors	Common	Uncommon
Preserved awareness	Common	Common if nondominant
Ictal laughing	Forceful, mirthless	Natural, mirthful
Secondarily generalized seizure	Common	Uncommon
Tendency for status epilepticus	Common	Uncommon
Postictal paresis	Common	Uncommon
Postictal confusion	Uncommon	Common

diagnosis of PNES. However, ictal EEG is normal in most epileptic auras and seizures without impairment of consciousness [35].

The VEEG Evaluation

The VEEG evaluation identifies interictal and ictal abnormalities, correlates clinical behavior and electrographic findings, and assists in the recognition of disabling or potentially injurious effects of ictal and postictal behaviors, such as seizure-induced cardiac arrhythmias. As in the case of seizure symptomatology, noninvasive (scalp) EEG in TLE generally reveals more localized and stereotyped features than in ExTLE, particularly FLE [28]. Temporal intermittent rhythmic delta activity localized to the temporal region is common in TLE. A unilateral focal preponderance of interical epileptiform discharges (IEDs) predicts the area of seizure origin with a probability of more than 95% [36]. Regional ictal EEG patterns are more appreciable in TLE (90%), specifically MTLE (93%), compared with ExTLE (50%), particularly mesial FLE (24%) [30]. An ictal pattern consisting of unilateral temporal rhythmic theta within 30 s of seizure onset correctly lateralizes the EZ in the vast majority of patients with TLE. Focal postictal slowing or attenuation more correctly lateralizes the side of seizure origin in TLE than in ExTLE.

VEEG manifestations of ExTLE often are the result of rapid propagation of epileptic activity into other areas, making it more difficult to localize the ictal onset. Movement artifacts due to vigorous motor activity stereotypic of some FLE cases may render the scalp EEG uninterpretable. The involvement of basal and mesial cortical areas not directly accessible to scalp EEG, rapid spreading of electric activity within and outside these areas, and tangential orientation of the spike source are responsible for the lower yield of scalp EEG in ExTLE [37]. Unifocal IEDs were found in only 21% of patients with refractory ExTLE; yet they highly predicted a localized ictal onset and good postsurgical outcome [38]. Lateralized, generalized, or nonlateralized ictal patterns are more common in ExTLE than TLE [30]. Generalized or multifocal IEDs typically preclude a surgical approach in adults. However, children and young adults with congenital or early acquired brain lesions with generalized, multifocal, or contralateral EEG abnormalities achieved postoperative outcomes similar to those with ipsilateral EEG abnormalities in one series [39••]. Additional electrode placements, including closely spaced scalp electrodes and sphenoidal electrodes, improve the yield of detecting IEDs from deep areas, including the mesial temporal, mesial frontal, and orbitofrontal regions. The VEEG evaluation aids in the diagnosis of patients with normal or inconclusive outpatient EEG recordings.

MRI

High-resolution MRI including sequences in orthogonal planes is required in the evaluation of patients considered for epilepsy surgery [40]. The yield of MRI in the detection of an epileptogenic lesion is increased further by using a specific MRI protocol tailored to the electroclinical information, obtaining images at a field strength of 3 T when the 1.5 T study is inconclusive, and detailed review by a radiologist with experience in epilepsy [41•]. Gradient echo/susceptibility-weighted imaging increases the sensitivity for occult calcified lesions and vascular malformations [42].

For HS, the most common pathology of TLE, the usual features on MRI are hippocampal atrophy (90%–95% of cases), increased hippocampal T2 signal intensity (80%–85%), loss of the internal hippocampal architecture (60%–95%), and decreased T1 signal intensity (10%–95%) [27]. In TLE, high-resolution MRI is negative in 30% to 40% of patients. However, 70% of patients with nonlesional TLE with a history of febrile seizures, unilateral temporal IEDs, and unilateral temporal ictal patterns achieved an excellent outcome after anterior temporal lobectomy [43]. MTLE-HS is a dynamic disease, which may explain why some patients do not display all the typical features of HS on MRI at the time of their presurgical evaluation.

Increased cortical thickness, abnormal gyral and/or sulcal patterns, poor gray-white junction differentiation, and gray matter signal abnormality on fluid-attenuated inversion recovery (FLAIR) and T2 sequences suggest a malformation of cortical development (cortical dysplasia), a common cause of intractable focal epilepsy, especially in ExTLE and in the pediatric population. Patients with concordant VEEG and MRI findings suggestive of an epileptic focus in noneloquent cortical areas generally are excellent epilepsy surgery candidates.

Nuclear Imaging

In the setting of discordant VEEG and MRI findings or negative high-resolution MRI, additional imaging often is required to identify surgical candidates. Metabolic imaging techniques include ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) and ictal SPECT, with the subtraction image coregistered to MRI (SISCOM) [44•]. ^{18}F-FDG, an indirect marker of neuronal activity, allows quantification of cerebral glucose metabolism to determine areas of dysfunction. Interictally, the epileptogenic focus and a surrounding brain area of variable size typically appear as a hypometabolic area. In MTLE-HS, ^{18}F-FDG-PET reveals ipsilateral hypometabolism in the mesial and anterolateral temporal areas, or bitemporal hypometabolism greater ipsilateral to the HS in 90% to 95% of cases. In patients with HS-negative TLE, ^{18}F-FDG-PET correctly lateralizes the epileptogenic zone in 86% of cases [45], decreasing to 40% in MRI-negative ExTLE cases [46].

Ictal SPECT visualizes the increased perfusion associated with ictal neuronal activity that occurs during epileptic seizures. This study is performed during a typical seizure during VEEG monitoring. Adequate timing of radioligand injection is required; an injection delay of 20 s or less from seizure onset correctly localizes to the area of ictal onset in most cases. In MTLE-HS, ictal SPECT shows ipsilateral anterior temporal hyperperfusion or bilateral but greater activity on the side of HS in about 90% of cases. Accurate localization of seizure foci ranges from 30% to 55% in ExTLE compared with 83% in TLE [47]. In TLE, ictal SPECT added value by correctly localizing the seizure focus in 77% of patients with nonlocalized ictal EEG and 80% of patients with nonlesional MRI [48].

Functional MRI

Functional MRI (fMRI) lateralizes speech and may provide localizing information of eloquent cortical areas, including primary motor and sensory cortices. Because of its noninvasive nature, fMRI has become the preferred method to determine language dominance over the intracarotid methohexital test or Wada test. In a recent study, the concordance between fMRI and Wada was better in patients with right TLE (89%) than in those with left TLE (73%), in whom left hemispheric language dominance was missed in 17% of cases [49]. The Wada test induces transient impairment in the brain territory supplied by the ipsilateral internal carotid artery, thereby uncovering essential contributions of the anesthesized territory to language and memory. It remains useful in select cases in which the proposed resection is believed to carry a substantial risk to language or memory functioning and in those with equivocal findings on fMRI.

Neuropsychology

Neuropsychological assessment uncovers material-specific impairment of memory and executive functions, thus providing localizing value and determining preserved function to guide the surgical plan. Patients with dominant TLE typically show impairment on measures of verbal memory, whereas those with nondominant TLE less consistently display deficits in visuospatial memory [50]. Impairment of executive function and attention is observed more often in FLE, although this information does not allow lateralization or further localization within the frontal lobe.

Conclusions

Patients with DRE and localizing findings on clinical history, seizure symptomatology, EEG, or neuroimaging are potential surgical candidates. The chances of successful epilepsy surgery increase with the number of concordant components of the presurgical evaluation. Importantly, the chances of sustained seizure freedom are lower in patients with DRE who continue receiving medical treatment alone, even compared with patients treated surgically who do not meet all the favorable outcome predictors. Because the chances of postsurgical seizure freedom decline with increasing age and disease duration, surgery should be considered as soon as drug resistance becomes apparent.

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