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Concept of epilepsy surgery and presurgical evaluation

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ABSTRACT – Epilepsy surgery is a well-accepted treatment for drug-resistant epilepsy. The success of the epilepsy surgery depends upon an appropriate presurgical evaluation process which should ensure the selection of suitable patients who are likely to become seizure-free following surgery without any unacceptable deficit. The two basic goals of the presurgical evaluation are the accurate localization and delineation of the extent of the epileptogenic zone, and its complete and safe resection. The process of the presurgical evaluation requires a multimodality approach wherein each modality provides unique and complimentary information which is combined with the information provided by other modalities to generate a hypothesis with regard to the likely epileptogenic zone. The basic modalities for the presurgical evaluation are clinical history, long-term video-EEG recording, high-resolution MRI, and neuropsychological evaluation. The additional modalities include functional imaging studies, electrical and magnetic source imaging, functional MRI, and intracranial monitoring. Each modality has its own limitations and the information provided by none of them is absolute. Hence, a concordance among the different modalities is the key to surgical success. The presurgical evaluation is a step-wise process starting form the most basic and most reliable tests and progressing to more complex and invasive modalities. The number of tests required varies according to the complexity involved and may include very basic minimum investigations in a given case, to the use of all the available investigations in more complex cases. The proper selection of various investigations and their accurate interpretation at each stage is required to ensure a successful outcome. In this article, we intend to review some of these basic concepts of presurgical evaluation and epilepsy surgery, and try to provide a frame work of the presurgical evaluation process.

Key words: drug-resistant epilepsy, epilepsy surgery, presurgical evaluation

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Pharmacotherapy with antiepileptic drugs (AEDs) remains the primary treatment for the epilepsies. Nevertheless, nearly 20% of patients with epilepsy continue to experience chronic recurrent seizures despite appropriate pharmacotherapy (Kwan and Schachter, 2011). Surgical treatment has the potential to eliminate seizures and improve the quality of life in a selected group of these patients with drug-resistant epilepsy (Engel, 1996; Schmidt and Stavem, 2009).

The practice of surgery to remove a part of epileptogenic cortex in order to make a patient seizure-free is not new. As early as 1879, William Macewen successfully localized and resected a frontal meningioma based on the semiology of the focal motor seizures (Macewen, 1879). Sir Victor Horsley has been credited with initiating the modern era of epilepsy surgery when he successfully localized and removed epileptogenic lesions in three patients with partial seizures at the London's National Hospital in 1886 (Horsley, 1886). However, it is only in the last three decades, with advances in modern diagnostic and therapeutic techniques, that epilepsy surgery has become increasingly recognized as a feasible treatment option for patients with drug-resistant seizures. Two randomized controlled trials (Wiebe *et al.*, 2001; Engel *et al.*, 2012) and several meta-analyses and systematic reviews (Engel *et al.*, 2003; McIntosh *et al.*, 2004; Tellez-Zenteno *et al.*, 2005; de Tisi *et al.*, 2011) have conclusively established the safety and efficacy of surgery in selected patients with drug-resistant epilepsy. The advances in structural and functional imaging and video-EEG (VEEG) monitoring, combined with simplification of intracranial electrode implantation techniques and the advent of neuronavigation and image-guided surgery, have widened the scope of epilepsy surgery, at the same time making it safer and less invasive. With an increase in the number of centres practicing epilepsy surgery on a regular basis, the number of patients being evaluated and selected for surgery has amplified. Still, surgery for epilepsy is one of the most underutilized therapeutic interventions in medicine and there are many challenges that need to be overcome to make epilepsy surgery pertinent to a wider patient population (Wiebe and Jetté, 2012; Engel, 2013).

Need for epilepsy surgery

Patients with drug-resistant epilepsy have considerable impairments in daily activities, education, employment, and social interaction due to continuing seizures and medication adverse effects (Lu and Elliott, 2012; Selassie *et al.*, 2014). These patients are at a higher risk of developing various psychological problems, such as depression, anxiety and psychosis (Dalmagro *et al.*, 2012; Hesdorffer *et al.*, 2012; Kanner *et al.*, 2012). Additional morbidity and mortality of the continued seizures include accidental injury, cognitive decline and sudden unexpected death in epilepsy (SUDEP) (Shorvon and Tomson, 2011; Surges and Sander, 2012; Ryvlin *et al.*, 2013b). Rates for employment, marriage and fertility are considerably lower in patients with poorly controlled seizures (Santosh *et al.*, 2007; Varma *et al.*, 2007; Luef, 2009). As a result, patients with drug-resistant epilepsy account for nearly 80% of the annual cost attributable to epilepsy (Cramer *et al.*, 2014). A select group of these patients with drug-resistant epilepsy has a real chance of becoming seizure-free with properly planned epilepsy surgery, with resultant benefits in quality of life.

Definition of drug-resistant epilepsy

The concept of medical refractoriness is pivotal for the selection of patients for presurgical evaluation and epilepsy surgery. It is generally agreed that an adequate trial of appropriate AEDs should be given before labelling the epilepsy as drug-resistant, at the same time avoiding the delay in surgery in indicated patients. However, the concept of adequate trials of AEDs is highly arbitrary and subjective. To overcome some of the ambiguity involved in defining drug-resistant epilepsy, the International League Against Epilepsy (ILAE) has proposed a consensus definition of drug-resistant epilepsy (Kwan *et al.*, 2010). According to this, drug-resistant epilepsy is defined as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom". Sustained seizure freedom is defined as seizure freedom for a minimum of twelve months or for a period three times the previous longest seizure-free period, whichever is longer. This definition places a greater emphasis on seizure freedom as this is the only meaningful outcome which can lead to sustained improvement in the quality of life. The definition equally emphasizes the importance of appropriate, informed and tolerated treatment schedules, as treatment failures due to inappropriately chosen or non-tolerated drugs, non-compliance to drugs, or unknown drug schedules cannot be classified as drug resistance. Failure of two AED schedules has been included in the definition with the recognition of the fact that subsequent chances of sustained seizure freedom are only modest (Kwan and Brodie, 2000). Patients fulfilling these criteria are candidates for detailed evaluation in a comprehensive epilepsy care program.

However, the definition should be applied in the proper clinical context and the effects of seizures on the patients' quality of life in terms of their psychological, interpersonal, and occupational functions should be taken into account while deciding intractability in clinical practice. A patient with infrequent but life-threatening seizures or seizures that impair occupational abilities can be considered to have drug-resistant epilepsy. Certain pitfalls also need to be avoided before making a diagnosis of drug-resistance. Every effort should be made to exclude seizure mimics and psychogenic non-epileptic events.

At the same time, pseudorefractoriness due to inadequate AED doses, inappropriate AED combinations or non-compliance should be excluded.

Surgically remediable epilepsy syndromes

With the recognition that certain forms of epilepsies with well-defined pathophysiological substrates and well-studied natural history have a poor prognosis after failure of few AEDs but have an excellent surgical prognosis, the concept of surgically remediable epileptic syndromes was introduced to promote early surgical intervention for these groups of epilepsies (*table 1*) (Engel, 1996). Mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS) is the most common type of focal epilepsy in adults and one that is most resistant to medical treatment and easiest to tackle surgically, with excellent post-operative seizure outcome (ILAE Commission, 2004). Epilepsies associated with cortical dysplasias, benign tumours such as ganglioglioma and dysembryoplastic neuroepithelial tumour, those with vascular malformations, and certain paediatric epilepsies associated with hemimegalencephaly and Rasmussen's encephalitis are other epilepsy syndromes in this category.

Table 1. Surgically remediable epilepsy syndromes categorized according to the degree of complexity involved in presurgical evaluation.

Patients who can be selected by non-invasive studies
- Mesial temporal lobe epilepsy associated with hippocampal sclerosis
- Circumscribed epileptogenic lesions (not near eloquent areas)
Benign neoplasms
Ganglioglioma
Dysembryoplastic neuroepithelial tumour
Low-grade astrocytoma
Oligodendroglioma
Vascular malformations
Atrophic scars
- Large unihemispheric epileptogenic lesions (for hemispherotomy)
Hemiconvulsion Hemiplegia Epilepsy (HHE)
Sturge-Weber syndrome
Rasmussen's encephalitis
Hemimegalencephaly
- Epileptic encephalopathies and multifocal disease (for corpus callosotomy)
Lennox-Gastaut syndrome
Patients who require functional imaging/mapping and/or invasive studies
- Temporal lobe epilepsy with
Discordant electroclinical data
Bilateral mesial temporal sclerosis
Normal MRI
- Extratemporal circumscribed epileptogenic lesions close to eloquent area
- Malformations of cortical development
- Dual pathologies

Selection of ideal candidates for epilepsy surgery

The main objective of the presurgical evaluation is to identify an abnormal area of cortex from which the seizures originate and to determine whether it can be removed without producing any significant functional impairment (Engel, 1996; Asano *et al.*, 2013). The goal of epilepsy surgery is to remove the minimal amount of tissue required to make the patient seizure-free, and no more. Certain rules should be followed before selecting or rejecting any patient for epilepsy surgery (*table 2*). The final success of epilepsy surgery depends upon the accurate delineation and complete removal of the "epileptogenic zone", which is defined as the area necessary and sufficient for initiating seizures, the removal or disconnection of which is necessary for abolition of seizures (Rosenow and Lüders, 2001). As a hypothetical concept, which can only be proven with postoperative seizure freedom, it is difficult to accurately define the epileptogenic zone preoperatively, but its boundaries can be approximated by identifying other important zones. These include: the symptomatogenic zone (cortical areas responsible for ictal symptoms), ictal onset zone (cortical area from where seizures originate), irritative zone

Table 2. Prerequisites and contraindications for epilepsy surgery.

Prerequisites
Drug-resistant seizures
Seizures causing significant social and medical disability
Reducing or stopping the seizures would result in a significant improvement in quality of life
Epileptogenic zone can be localized with convergent data from different investigative modalities
Acceptable risk-benefit ratio for surgery
Relative Contraindications
Primary generalized epilepsy
Minor seizures not impairing the quality of life
Progressive medical or neurological disorder
Active psychosis, not related to peri-ictal period
Behavioural problems that impair rehabilitation
Poor contralateral memory function (for temporal lobectomy)

(cortical areas generating interictal spikes), lesional zone (area showing lesion on MRI), and functional deficit or hypofunctional zone (areas of brain showing interictal dysfunction).

These zones and dysfunctions can be identified using different modalities, namely clinical history (symptomatogenic and hypofunctional zones), neuropsychological testing (hypofunctional zone), interictal and ictal scalp EEG (irritative zone and ictal onset zone), structural MRI (lesional zone), interictal positron emission tomography (PET; hypofunctional zone), and ictal single photon emission computed tomography (SPECT; ictal onset zone). These can be further supplemented by identifying the important functional areas using functional MRI, cortical stimulation and mapping (functional deficit zone), and Wada testing. As all the different modalities provide different information and the information provided by none of the modalities is absolute, the chances of surgical success increase with increasing concordance between different modalities (Engel, 1999; Rosenow and Lüders, 2001; Asano *et al.*, 2013). In cases with more than one presumed epileptogenic zone, such as patients with bilateral hippocampal sclerosis or patients with tuberous sclerosis with multiple tubers, surgery is possible if all or a majority of seizures can be proven to arise from one side or from two different non-homotopic regions.

Presurgical evaluation

Comprehensive epilepsy care facility

As the presurgical evaluation involves multiple diagnostic modalities, a close collaboration between different disciplines and teamwork is essential to run a successful epilepsy surgery program. The main challenge in the management of patients with drug-resistant epilepsy is to address the medical and psychosocial issues together, which requires a multidisciplinary approach. Patients with drug-resistant epilepsy usually have associated psychological and behavioural problems including depression, anxiety and even major psychosis (Dalmagro *et al.*, 2012; Hesdorffer *et al.*, 2012; Kanner *et al.*, 2012). They may have psychogenic non-epileptic events, either in isolation or associated with true seizures. These patients are often unemployed and are not motivated for gainful employment. Proper psychological counselling and vocational training can improve these issues. Preoperative vocational training also improves the chances of postoperative employment. It is often necessary to consult psychologists, psychiatrists, occupational therapists and social workers during the process of the presurgical evaluation. These, along with the neurologists, neurosurgeons, radiologists, trained EEG technologists and epilepsy nurses, constitute an organized team of the comprehensive epilepsy care program.

Presurgical evaluation strategy

As discussed above, presurgical evaluation is a multidisciplinary team approach. The extent of presurgical evaluation required in an individual case varies according to the degree of complexity involved (Engel, 1999; Rosenow and Lüders, 2001; Asano *et al.*, 2013). A patient with clinical features of mesial temporal lobe epilepsy and confirmed unilateral mesial temporal sclerosis on MRI only requires VEEG monitoring to verify the ictal onset zone and to rule out non-epileptic seizures, while a patient with extratemporal seizures and normal MRI may require all available investigations, including invasive monitoring. Presurgical evaluation is usually performed in a step-wise manner, with more complicated cases requiring more invasive and complex investigations to define the ictal onset zone.

The primary components of the presurgical evaluation include a detailed clinical history and physical examination, video-EEG monitoring, advanced neuroimaging, neuropsychological testing, and assessment of psychosocial functioning.

The second stage may include functional studies, such as SPECT and PET, and other modalities, such as magnetic source imaging (MSI), EEG-functional MRI (EEG-fMRI), and electrical source imaging (ESI), while intracranial monitoring is reserved as a last stage. The other important part of the presurgical evaluation is to predict and minimize the postoperative functional deficits. The various modalities used for this purpose are the Wada test and functional MRI for language and memory functions, and cortical stimulation and mapping during intracranial monitoring.

While all these facilities are easily available in high-income countries, epilepsy surgery centres in low- and middle-income countries usually lack the full range of technologies to perform presurgical evaluation. Therefore, the success of an epilepsy surgery program in a resource-constrained set-up will depend upon the ability to select ideal surgical candidates using locally available technology and expertise, without jeopardizing patient safety (Sylaja and Radhakrishnan, 2003). The usual step-wise protocol for presurgical evaluation is outlined in *table 3* and *figure 1*, and is further illustrated through *figures 2* to *5*.

Clinical evaluation

The basic aim of the detailed clinical evaluation is to obtain reliable information about seizure semiology and to postulate the likely aetiology, and to ascertain

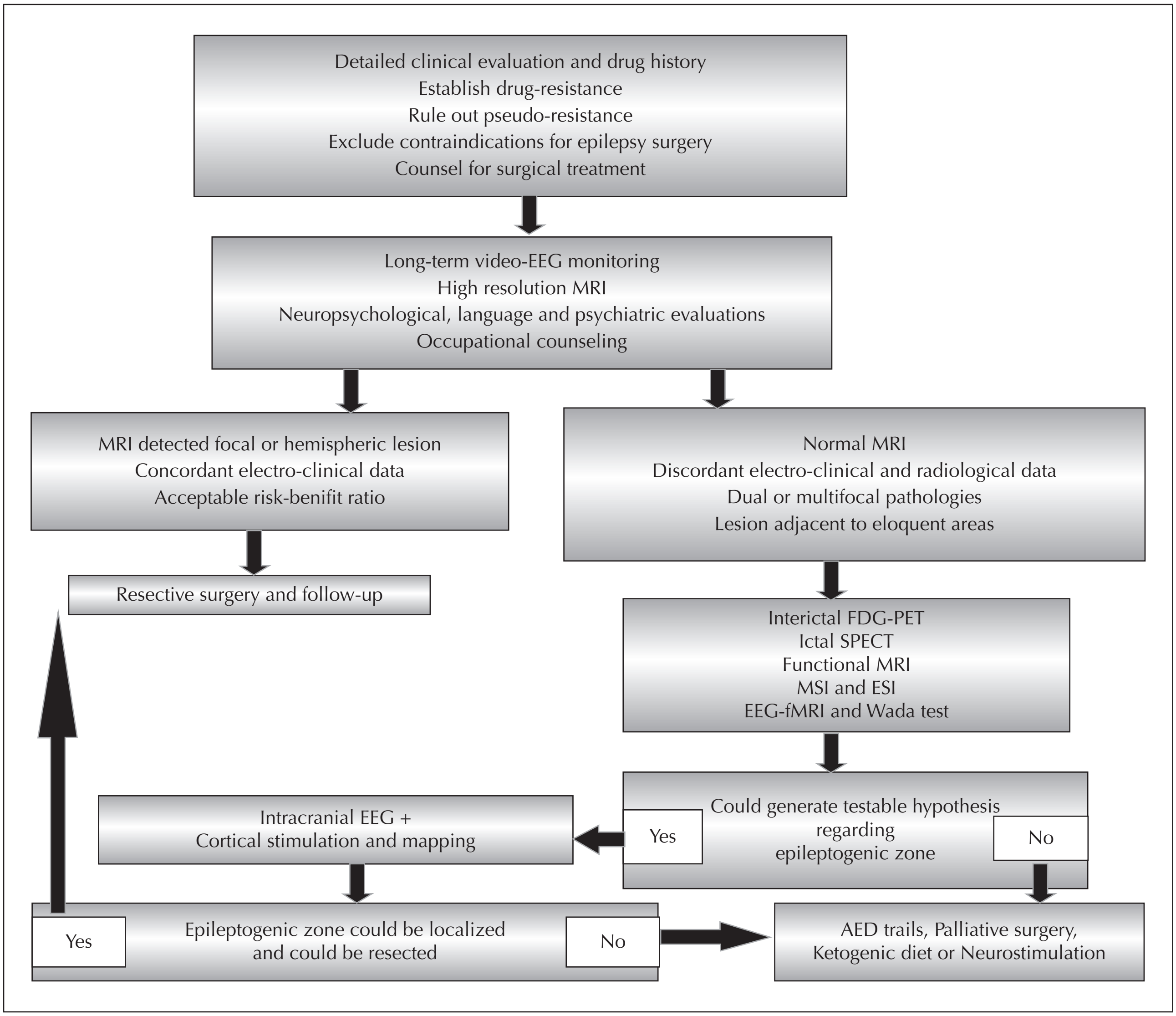

Figure 1. Flow chart depicting the usual process of presurgical evaluation and selection for surgery (reproduced with permission from Rathore *et al.*, 2014).

adequacy of AED therapy and impact of seizures on the quality of life. A detailed inquiry regarding the presence of various risk factors for epilepsy, including perinatal injury, febrile seizures, meningoencephalitis and head trauma, can provide valuable information about the likely aetiology of epilepsy. The presence of childhood febrile seizures followed by a latent period of several years and the subsequent appearance of complex partial seizures of temporal lobe semiology strongly suggests the possibility of hippocampal sclerosis as the underlying aetiology for epilepsy. Subtle deficits based on physical examination, such as mimic facial palsy (Jacob *et al.*, 2003), visual field deficits and hemiparesis provide important localizing and lateralizing information.

Long-term video-EEG monitoring

Long-term VEEG monitoring provides information about seizure semiology, interictal abnormalities, and ictal rhythms. It is a definitive method to differentiate between seizures and non-epileptic events, classify seizures, and localize the ictal onset zone. Careful interpretation of the focal interictal epileptiform discharges (IEDs) provides useful localizing information. The IEDs and temporal intermittent rhythmic delta activity (TIRDA) confined to one temporal region in a patient with MTLE are predictive of good surgical outcome (Williamson *et al.*, 1993; Radhakrishnan *et al.*, 1998; Serles *et al.*, 1998). However, 10% of patients with temporal lobe epilepsy and one third of patients with

Table 3. Different investigative modalities used during presurgical evaluation.

Basic evaluation
Detailed clinical evaluation
Long-term scalp video-EEG monitoring (semiology, interictal & ictal EEG)
1.5T/3T MRI
Neuropsychological evaluation
Psychosocial and psychiatric evaluation
Language evaluation
Occupational evaluation and counselling
Additional evaluation (in selected cases)
For Source localization
Novel MRI contrasts and post-processing techniques
Interictal & ictal SPECT co-registered to MRI (SISCOM)
FDG-PET
EEG-fMRI
Magnetic source imaging
Electrical source imaging
Electrocorticography
Intracranial EEG
For predicting and minimizing postoperative deficits
Functional MRI (motor, sensory, language, memory)
Wada test
Diffusion tensor imaging (DTI) and tractography
Cortical stimulation and mapping

SPECT: Single photon emission computed tomography; FDG-PET: 18-flourodeoxyglucose positron emission tomography; fMRI: functional MRI.

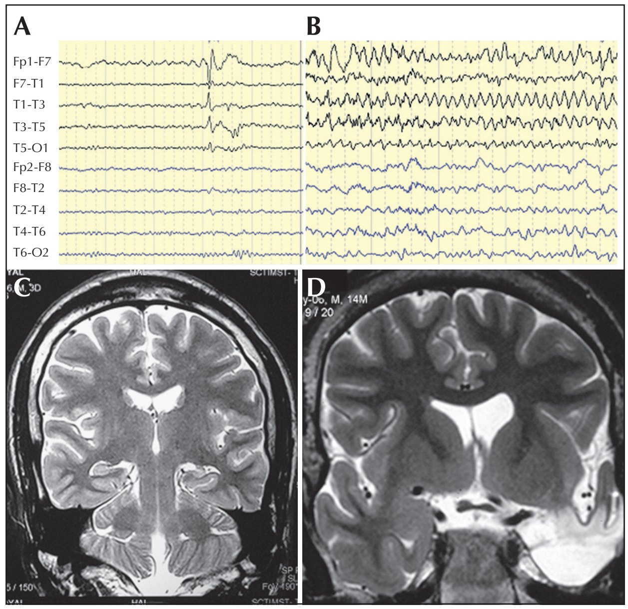

Figure 2. The EEG-MRI data from one of the operated patients: (A) EEG showing left temporal interictal epileptiform discharges; (B) 7-Hz-rhythmic theta activity over the left temporal region; (C) left hippocampal atrophy and increased signal on T2-weighted MRI sequence; and (D) postoperative MRI showing complete resection of mesial temporal structures. The patient was seizure-free for over five years following left anterior temporal lobectomy with amygdalo-hippocampectomy.

frontal lobe epilepsy may not have any IEDs during VEEG monitoring (Williamson *et al*., 1993; Vadlamudi *et al*., 2004). On the other hand, IEDs are usually more widespread than the ictal onset zone, especially in children. Around 20-30% of patients with MTLE may have bitemporal IEDs, although ictal onset zone is usually confined to one temporal region (Serles *et al*., 1998). Patients with mesial occipital lobe epilepsy or mesial frontal epilepsy can have bilateral, generalized or sometimes contralateral IEDs (Salanova *et al*., 1992; Vadlamudi *et al*., 2004). While temporal IEDs are relatively frequent in patients with frontal and posterior quandrantic epilepsies, the presence of extratemporal IEDs in a patient with features of MTLE may suggest a possibility of pseudo-temporal or temporal-plus epilepsies (Lee *et al*., 2003; Barba *et al*., 2007). Persistent focal interictal abnormalities in a patient with West syndrome or in tuberous sclerosis with multiple lesions may provide the evidence of focal pathology, which can be detected by structural or functional imaging and may be amenable to surgical resection.

Both the VEEG-recorded seizure semiology and ictal patterns provide information on localizing the ictal onset zone. Certain clinical features have been recognized to have useful lateralizing or localizing value (*table 4*) (Loddenkemper and Kotagal, 2005; So, 2006). Careful interpretation of sequential semiological features in isolation and in clusters along with EEG correlation is important for correct localization, as none of the semiological features are absolute. The same also holds true for ictal rhythms which can be relatively variable and the need for the careful analysis of frequency, morphology and distribution cannot be overemphasized. Prototype ictal pattern for a mesial temporal seizure is 5-7-Hz rhythmic theta activity over the temporal electrodes (Ebersole and Pacia, 1996). Neocortical seizures usually begin as focal or lateralized delta activity, beta activity or lateralized suppression. Extratemporal seizures are usually brief and have a tendency for rapid spread and hence are more difficult to localize than temporal seizures. In patients with large hemispheric abnormalities, such as porencephalic cyst, IEDs and ictal onset may be generalized or even seen over the contralateral hemisphere (Wyllie *et al*., 2007). A correlation with other investigations is necessary for final localization.

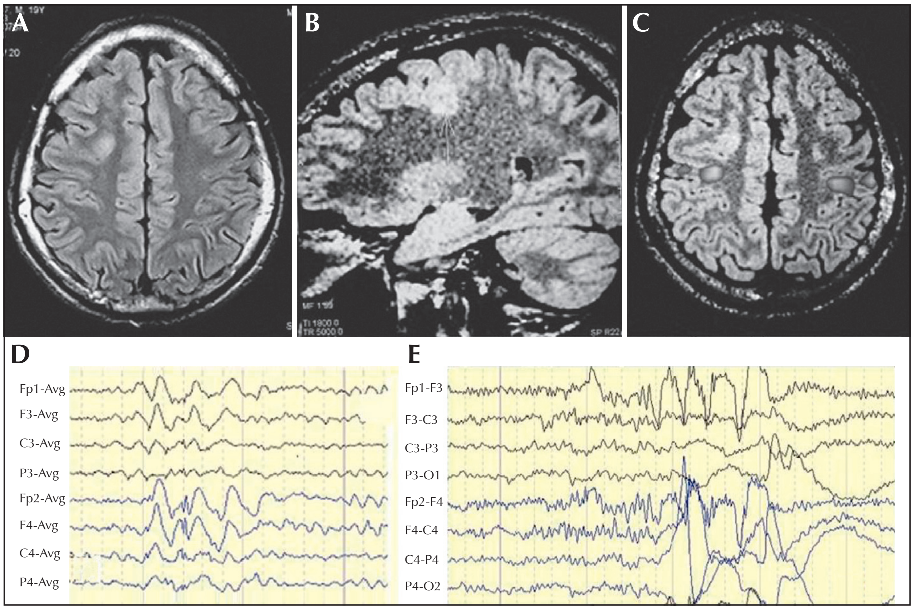

Figure 3. Presurgical non-invasive data from a patient with drug-resistant frontal lobe epilepsy: (A) axial FLAIR image showing thickened cortex and signal changes over the right frontal region; (B) saggital 3-D FLAIR image showing extension of the lesion to periventricular region (transmantle dysplasia); (C) functional MRI showing left hand motor function immediately posterior to the lesion; (D) interictal recording showing right frontal spike discharges; and (E) ictal EEG recording showing right frontal beta activity at the onset of a complex partial seizure. The patient did not develop any neurological deficit following lesion resection and has been seizure-free for the last five years.

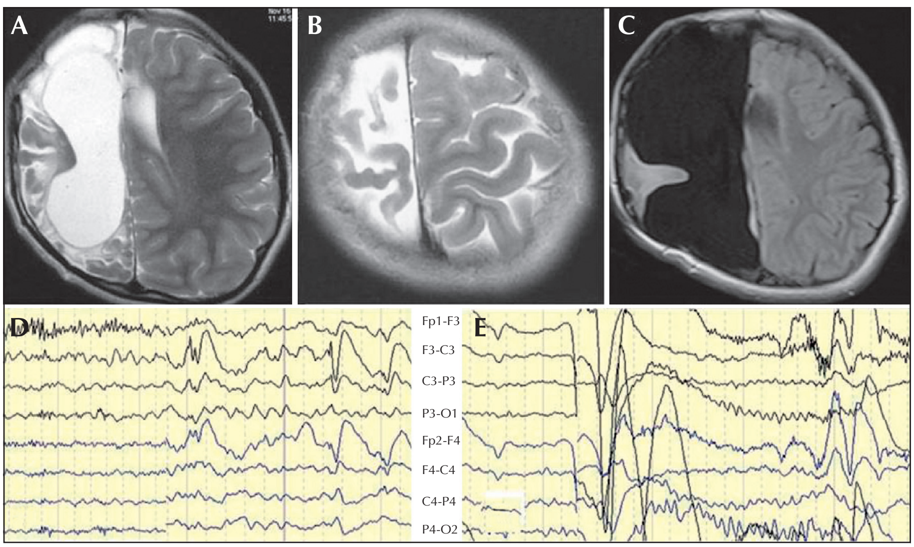

Figure 4. Presurgical data from a patient with drug-resistant seizures and minimal weakness of the left hand: (A, B) T2-weighted axial MRI sequences showing extensive encephalomalacia over the right hemisphere with relatively preserved motor cortex; (C) postoperative axial FLAIR image following hemispherectomy with preservation of motor cortex; (D) interictal EEG showing relative suppression of background activity over the right hemisphere with bifrontal spike-and-wave discharges which appeared more prominent over the left frontal region; and (E) ictal EEG showing diffuse attenuation of background activity for one second, followed by appearance of diffuse 14-Hz activity. The patient was seizure-free for two years without any additional motor deficits.

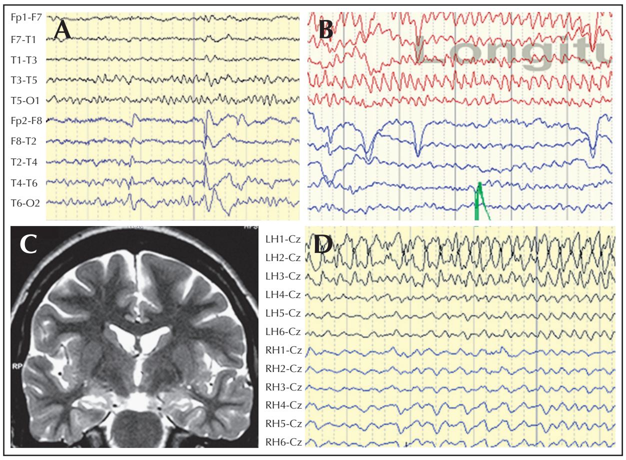

Figure 5. Invasive evaluation in temporal lobe epilepsy:
(A) interictal scalp EEG showing right temporal spike discharges;
(B) ictal scalp EEG showing left temporal 6-Hz rhythmic theta activity during a complex partial seizure;
(C) T2-weighted coronal MRI showing bilateral mesial temporal sclerosis, slightly more pronounced on the left side; and
(D) invasive EEG monitoring with bilateral hippocampal depth electrodes (inserted orthogonally in postero-anterior direction; LH1: left hippocampal contact 1) showed origin of all the 11 recorded seizures form the left hippocampus. Neuropsychological evaluation revealed predominant verbal memory impairment. The patient has been seizure-free for the last four years and did not have any significant worsening of memory.

Table 4. Lateralizing value of semiology of seizures.

Contralateral hemisphere
Dystonic limb posturing or paucity of limb movements
Asymmetric tonic limb posturing (figure of 4 sign)
Tonic head version before secondary generalization
Unilateral clonic jerking
Ipsilateral hemisphere
Postictal nose wiping
Asymmetric ending of late clonic phase
Unilateral eye blinking
Unilateral automatisms
Early eye and head deviation
Non-dominant hemisphere
Ictal speech
Preserved speech with bilateral manual automatisms
Ictal cough, vomiting and spitting
Dominant hemisphere
Ictal speech arrest
Postictal dysphasia lasting for more than 2 minutes

Gradual reduction of AEDs is required during long-term VEEG monitoring for the induction of seizures. The number of seizures required for the selection of patients for surgery varies between studies and among the centres. In a patient with strictly unilateral MTLE, recording one or two habitual seizures is sufficient, while in patients with features of bitemporal epileptogenicity, at least five seizures of unitemporal origin are necessary to be fairly certain that a patient has unifocal seizure origin (Blume, 1994). Some patients considered for focal resections, such as those with mesial temporal lobe sclerosis and circumscribed focal lesions away from eloquent areas, and those with large hemispheric lesions considered for hemispherotomy, could be selected for surgery based on the concordance of clinical, structural imaging, and interictal EEG data, and may not always require ictal video-EEG recordings (Cambier *et al*., 2001; Monnerat *et al*., 2013; Rathore *et al*., 2014). This could be an alternative approach in resource-poor countries with extremely limited access to continuous video-EEG monitoring. However, such strategies should be used only by highly experienced professional teams, either available locally or in consultation with experts from well-established epilepsy surgery centres elsewhere. The concept of omitting ictal recording in selected patients remains controversial and the present standard of care includes ictal recordings for all patients undergoing presurgical evaluation.

Precipitating seizures by AED withdrawal for VEEG monitoring is not without the risk of sudden unexpected death in epilepsy (SUDEP). A recent systematic retrospective survey of epilepsy monitoring units located in Europe, Israel, Australia and New Zealand (MORTEMUS study) showed a SUDEP incidence of 1.2 (0.6-2.1) per 10,000 VEEG monitorings, probably related to inadequate supervision and possibly to AED withdrawal (Ryvlin *et al*., 2013a). It is important to ensure optimal organization of epilepsy monitoring units (EMUs), especially continuous supervision by a dedicated staff, which is not adhered to by a quarter of European and US-based EMUs (Rheims and Ryvlin, 2014).

Structural and functional imaging

Complete removal of the MRI-detected structural lesion is the most important factor determining seizure freedom following surgery (Berkovic *et al*., 1995; Radhakrishnan *et al*., 1998). This makes MRI the most important tool in the presurgical evaluation. The most important advances in the field of epilepsy surgery have been in structural imaging, allowing the detection of subtle abnormalities (Duncan, 2010; Jackson and Badaway, 2011). However, caution should always be exercised to define the cause-effect relationship between the MRI-detected abnormality and the seizures. Patients with extratemporal epilepsies may have non-specific secondary hippocampal atrophy or dual pathology (Cendes *et al.*, 1995; Rathore *et al.*, 2012). Common lesions in patients with refractory epilepsy are mesial temporal sclerosis, focal cortical dysplasias, and benign neoplasms. About 20-30% of patients with classic temporal lobe epilepsy do not have any MRI-defined abnormality (Berkovic *et al.*, 1995; Radhakrishnan *et al.*, 1998; Sylaja *et al.*, 2004). Various methods, such as hippocampal volumetry, T2 relaxometry, magnetic resonance spectroscopy, and peri-ictal diffusion-weighted MRI, have been developed to detect subtle abnormalities in these patients (Knake *et al.*, 2005; Duncan, 2010; Jackson and Badaway, 2011). Newly developed MRI techniques and post-processing methods, such as the use of phased array surface coil and higher MRI fields (3T), double inversion recovery, magnetization transfer imaging, fast FLAIR T2, 3-D and curvilinear reformatting, and diffusion tensor imaging (DTI) analyzed with voxel based approaches, can be used to identify focal lesions in many patients with normal conventional MRI (Duncan, 2010; Jackson and Badaway, 2011). The DTI and tractography can help in minimizing the postoperative deficits following epilepsy surgery by delineating the white matter tracts in the vicinity of the lesion (Radhakrishnan *et al.*, 2011).

The functional MRI has two important uses in the management of epilepsy:

– to identify eloquent areas in relation to an epileptic lesion being considered for resection;

– to detect fMRI activity in relation to interictal epileptic spikes on EEG that may be helpful in the localization of seizure focus.

Functional MRI for language, motor and sensory tasks have been well standardized and are routinely used to minimize the deficits while planning resection near these eloquent areas (Petrella *et al.*, 2006; Kesavadas *et al.*, 2007). Recently, memory fMRI has been shown to predict postoperative memory outcome in patients undergoing temporal resections (Powell *et al.*, 2008). Spike-related blood oxygen level dependent (BOLD) activation can be used for source localization by simultaneous continuous fMRI with scalp EEG recording (EEG-fMRI). A few small clinical studies have demonstrated its utility in source localization, in addition to the conventional tools (Thornton *et al.*, 2010). However, more large scale validation studies are required before its routine use in clinical practice.

The main indication for functional imaging methods, such as SPECT and 18-flouro-deoxyglucose PET (FDG-PET), is to provide localizing information for patients when baseline non-invasive investigations are either non-localizing or discordant. These can help in guiding invasive monitoring in patients with normal MRI or with multifocal or diffuse MRI abnormalities. Ictal SPECT can provide the localizing value in 70-90% of temporal lobe seizures and 60% of extratemporal epilepsies (So and O'Brien, 2012). However, its utility in providing information over and above the other baseline data is rather modest (Rathore *et al.*, 2011). Many factors such as timing of injection, duration of the seizure, and generalization during the seizure can affect the interpretation of SPECT data, necessitating its use in conjunction with other modalities. Certain recent advances in the post-acquisition processing of the SPECT images, such as subtraction ictal SPECT co-registered to MRI (SISCOM) and statistical parametric mapping (SPM), have enhanced its value (So and O'Brien, 2012). FDG-PET can provide the lateralizing information in about 60-90% of temporal lobe epilepsies (O'Brien *et al.*, 2008). This is especially useful in cases with normal MRI, where a PET study combined with other non-invasive investigations can obviate the need for invasive monitoring (LoPinto-Khoury *et al.*, 2012). However, FDG-PET usually shows more widespread hypometabolism than the actual ictal onset zone and caution is needed while interpreting the results. Interictal FDG-PET is less sensitive in extratemporal epilepsies but can provide useful localizing information to guide intracranial monitoring in patients with normal MRI. Alpha-methyl-L-tryptophan PET has been shown to be effective in differentiating between epileptogenic and non-epileptogenic lesions in patients with tuberous sclerosis (Juhasz *et al.*, 2003).

Neuropsychological evaluation and the Wada test

Apart from providing the valuable information regarding the lateralization and localization of the seizure focus, neuropsychological assessment is the best single means of quantifying the cognitive abilities and psychosocial status of a person (Sawrie *et al.*, 1998; Jeyaraj *et al.*, 2013). The information obtained through neuropsychological testing helps in counselling patients about potential risk of postoperative memory impairment. Additionally, neuropsychiatric assessment is an essential part of presurgical evaluation to detect and treat the associated depression, anxiety and psychosis.

Though the Wada test still remains the gold standard for determining the hemispheric dominance for language functions, functional MRI is increasingly replacing it (Binder *et al.*, 1996). Its role in predicting memory outcome following temporal lobectomy is being increasingly questioned and many centres have abandoned its use as a routine test before temporal lobectomy (Kirsch *et al.*, 2005; Baxendale *et al.*, 2008; Rathore *et al.*, 2013). Non-invasive evaluation with fMRI, PET and MEG may largely obviate the need for the Wada test in the future.

Magnetic and electrical source imaging (MSI and ESI)

Magnetoencephalography (MEG) combined with source modelling and co-registered to MRI, called magnetic source imaging (MSI), can provide the source localization of the interictal spikes (Stefan *et al*., 2003). Its indications are more or less the same as those of SPECT and PET. In one of the largest validity studies in which localizing values of MSI, PET and SPECT were evaluated in relation to the surgical outcome in patients with non-localizing or discordant information on MRI and VEEG, MSI had a sensitivity of 55% and specificity of 72% which was similar to PET and SPECT (Knowlton *et al*., 2008). All three modalities, however, provided complementary information in different patients. Other studies have also shown that postoperative seizure outcome is better if the MSI-identified dipole area is included in the resection (Genow *et al*., 2004). MSI can also help in the localization of stimulus-induced normal neuronal function. This can be used for mapping the location of somatosensory, motor, language and other cognitive functions while planning surgical resection.

The ESI is a source modelling technique which utilizes realistic head models and inverse source estimation methods to detect the source of EEG spikes. It can improve the spatial resolution of EEG signals and can provide better source localization than the EEG. In a large clinical series of 152 operated patients, the localizing value of ESI was compared with other modalities (Brodbeck *et al*., 2011). ESI was found to have a sensitivity of 84% and a specificity of 88% if the EEG was recorded with a large number of electrodes (128-256 channels) and the individual magnetic resonance image was used as head model. The utility was lower if the number of electrodes was less. Overall, ESI is an additional emerging toll in the presurgical evaluation.

Intracranial monitoring

Intracranial monitoring is indicated when the results of non-invasive methods are conflicting or non-contributory. In patients with suspected MTLE, it is broadly indicated in four scenarios in patients with:
- normal MRI;
- bilateral mesial temporal sclerosis on MRI;
- dual pathology;
- electroclinical discordance where either of the investigations is equivocal or contradictory, as in suspected wasted hippocampal syndrome (Pacia and Ebersole, 1999).

Judicious use of sphenoidal electrodes during VEEG recording can obviate the need for invasive EEG monitoring in nearly one in five patients with suspected MTLE (Cherian *et al*., 2012). In extratemporal epilepsy, invasive monitoring is indicated in order to define the epileptogenic zone in patients with indistinct or very large lesions, or when the suspected epileptogenic zone is located in or near eloquent cortex, such that extensive extraoperative cortical stimulation studies are required to confirm its relationship with eloquent cortex (Sperling, 1997; Asano *et al*., 2013). A detailed description of intracranial monitoring is beyond the scope of this review and readers should consult the literature for further information.

Conclusions

Surgical therapy has the potential to improve the quality of life in selected patients with drug-resistant epilepsy. Success of the epilepsy surgery depends on the precise localization and delineation of the extent of the epileptogenic zone, and its complete and safe removal. The process of presurgical evaluation is a multistage process which utilizes different modalities depending upon the complexity involved in a given case. As information provided by none of the modalities can be considered absolute, careful interpretation of data obtained through each modality is essential to gain the required information in a cost-effective manner and to maximize the chances of good post-operative outcome. □

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What are the common aetiologies for refractory epilepsy?

(2) What are the basic investigative modalities utilized during presurgical evaluation?

(3) When is intracranial monitoring required in patients with mesial temporal lobe epilepsy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".