



Presurgical evaluation for drug refractory epilepsy



Manjari Tripathi^{a,*}, Sucharita Ray^a, P. Sarat Chandra^b

^a Department of Neurology, All India Institute of Medical Sciences (AIIMS), New Delhi, 110029, India

^b Department of Neurosurgery, All India Institute of Medical Sciences (AIIMS), New Delhi, 110029, India

HIGHLIGHTS

- Presurgical evaluation for drug refractory epilepsy must be multimodal.
- Basic investigations are a video EEG documenting 3 habitual seizures more seizures must be recorded if there are multiple lesions, combination with pseudoseizures, normal MRI and discordance in localization between these.
- A 3 Tesla epilepsy protocol MRI which is electroclinically guided to its reading is a must.
- When there is discordance of these basic investigations or when the MRI is normal and shows multiple lesions- PET, Ictal and interictal SPECT (SISCOS) and MEG must be done.
- When the hypothesis is clear but not sufficient to go for direct surgery Stereo EEG implantation and grids (for mapping eloquent cortex) specially should be used.

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ABSTRACT

Surgical management of epilepsy is an established safe and effective way in improving patients' seizure frequency and overall morbidity. A robust array of options is available to carry out an in-depth evaluation of a surgical candidate in epilepsy. However, underutilisation of the available options may seriously challenge post-operative outcomes. In this paper, we discuss the different aspects of various non-invasive and invasive procedures available to evaluate a surgical candidate of epilepsy and discuss their relative advantages and position in the diagnostic algorithm.

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1. Introduction

Surgery for epilepsy is an established method for substantial reduction in seizure frequency and improvement in the quality of life of the patient. Although associated with inherent risks, the collaterals weigh less than the risk of uncontrolled seizures. The morbidity and mortality of seizures even if small (about 0.5%) is cumulative every year. Thus a person having 6 years of seizures will

have a risk of 3% mortality [1]. Adequate safety of epilepsy surgery has been proven in a majority of world literature an attendant the risk of death being no more than 2%. Thus it is not illogical to consider epilepsy surgery if the seizures are therapy resistant. Other causes to consider surgical intervention include: Fig. 1.

- cognitive decline accruing due to recurrent epilepsy is seen with certain epilepsy syndromes or status epilepticus (SE) [2].
- depression occurring in up to 9–37% and anxiety in up to 11–25% patients with medically refractory epilepsy mandates emergent redressal [3].

* Corresponding author. Department of Neurology, Room No 705, Neurosciences Centre, All India Institute of Medical Sciences, New Delhi, 110029, India.

E-mail address: mtripathiaiims@gmail.com (M. Tripathi).

Abbreviations

AED	Antiepileptic drug
AIIMS	All India Institute of Medical Sciences
AMTR	Anteromedial temporal resection
Cm	Centimeter
CT	Computerized Tomography
DRE	Drug-resistant epilepsy
ECoG	Electrocorticogram
EEG	Electroencephalogram
e.g	For example
etc	et cetera
fMRI	Functional Magnetic Resonance Imaging

FDG	Fluorodeoxyglucose
Hz	Hertz
ILAE	International League Against Epilepsy
LKS	Landau-Kleffner syndrome
ml	milliliter
MRI	Magnetic Resonance Imaging
MTS	Mesial Temporal Sclerosis
PCO2	Partial pressure of carbon dioxide
PET	Positron emission tomography
SE	Status epilepticus
SISCOM	Subtraction ictal-interictal SPECT coregistered to MRI
SPECT	Single-photon emission tomography

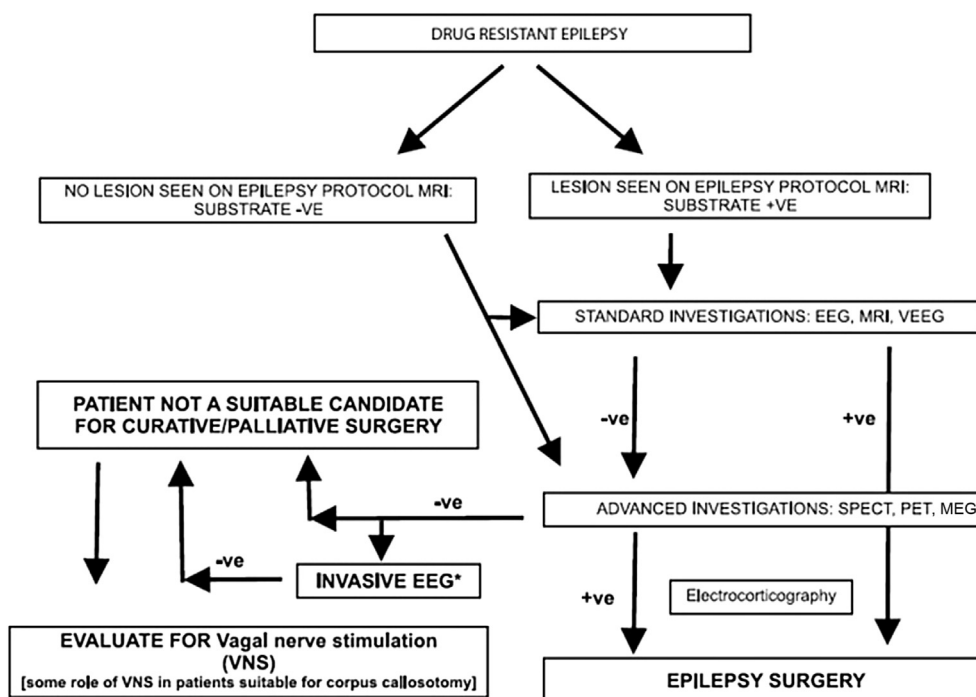


Fig. 1. Flowchart showing a management algorithm for patients being subjected to epilepsy surgery.

- c) vocational issues impeding employment
- d) social stigma associated with epilepsy, seen particularly in developing countries like India, and hence early surgery when indicated may be advantageous.
- e) better long term economic feasibility in the patient undergoing early surgery

In several retrospective trials and one prospective, randomized, controlled trial for a well-defined.

syndrome with a known favorable surgical outcome, surgery was demonstrated to have less morbidity and mortality. In addition, surgery also yielded a better quality of life and reduced depression and anxiety as early as three months after anteromedial temporal resection (AMTR), compared with continued medical therapy. This improved quality of life is specifically related to the occurrence of complete seizure freedom in both the medical and surgical study groups [1].

In order to undertake such a fruitful and successful procedure,

appropriate selection of candidates is a must along with their complete and thorough workup to maximize the benefit of surgery. In fact, the presurgical evaluation of the candidate to determine the suitability of the candidate for surgery is almost as important as selecting the correct surgical procedure for the candidate to improve morbidity and mortality outcomes.

1.1. Strategy for a surgical workup

The presurgical evaluation for epilepsy has changed substantially in the past few.

decades, most notably since the advent of long-term video-EEG monitoring in the late.

1970s, advanced neuroimaging, and subspecialty epilepsy centers. It is a coordinated input of an integrated team consisting of neurologists, neurophysiologists, neuropsychologists, social workers, radiologists, nurses, and epilepsy neurosurgeons. Aspects of the presurgical evaluation include patient's clinical history and

physical examination findings, social circumstances, seizure syndrome and severity along with diagnostic testing findings. A surgical plan is usually developed at a multidisciplinary team conference. This allows open discussion among multiple experts so that the surgical approach is unique and is tailored to the individual's personal needs and epilepsy syndrome. When all pre-surgical information points to a unifying location and theory regarding focal seizure onset (also referred to as concordant data), then the patient may proceed directly to respective surgery. When data are inadequate to define a respective strategy, then diagnostic intracranial electrodes may be considered to further define the syndrome or site of seizure onset prior to any resective surgery (phase II) [4].

2. Diagnostic phase

A presurgical diagnosis is made after classifying the seizure types and specific epilepsy syndrome affecting the patient. The International League Against Epilepsy (ILAE) recognizes approximately ten types of recurrent seizures and approximately forty forms of epilepsy syndromes [5]. Both classification schemes reflect the fact that seizures and epilepsies naturally fall into two major groups, based on the site of seizure onset in the brain, either (1) focal (partial, localization-related) or (2) generalized [6].

2.1. Structural and metabolic brain imaging

Because seizures may result from cortical lesions or malformations, neuroimaging can often help identify and localize this damage and, therefore, the focus.

2.1.1. Computerized tomography (CT) scanning

Not used in routine practice. Magnetic Resonance imaging (MRI) has replaced routine CT scanning because of superior imaging resolution. The one exception is that CT scanning demonstrates intraparenchymal calcification and acute bleeding better than MRI. It is also much more rapid process compared to MRI which takes more time. This may be helpful in distinguishing certain types of tumors or CNS syndromes, such as Sturge Weber syndrome and calcifications. The sensitivity of CT has not been found to be higher than 30% in unselected patient populations [7].

2.1.2. MRI

Brain MRI unquestionably is the best structural imaging study. Every surgical evaluation should include a complete study with special thin-cut magnified views perpendicular to the axis of the temporal horn. These views can demonstrate mesial temporal sclerosis (MTS) in children and adults and developmental malformations in infants and young adults. MRI can detect up to 80% cases of patients with refractory focal epilepsy and about 20% patients with a single unprovoked seizure or epilepsy in remission [8,9].

2.1.3. Positron emission tomography (PET)

Unlike MRI or CT scanning, PET scanning demonstrates brain glucose metabolism rather than structure. The typical finding from an interictal scan is hypometabolism in the region of the epileptic focus and, if the scan is obtained during a seizure, the typical finding is hypermetabolism from the focus. PET is more sensitive in temporal compared to extratemporal lobe epilepsy with a sensitivity of up to 70–80% [10].

2.1.4. Single-photon emission tomography (SPECT)

SPECT scanning helps quantify as well as visualize the blood flow through a region of the brain thus allowing for both qualitative and quantitative evaluation of regional cerebral perfusion [11].

Interictal SPECT scans are less accurate than ictal scans. However, ictal scans are problematic because the tracer must be injected within the initial seconds of seizure onset. This requires that the radionuclide is available on the monitoring ward 24 h per day with personnel licensed (under state law) to administer intravenous injections. Ictal F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) can provide better spatial resolution than single photon emission CT by better delineation of seizure onset zone and propagation pathways [12].

2.1.5. A newer methodology that has greater accuracy than either ictal or interictal SPECT scanning is subtraction ictal-interictal SPECT coregistered to MRI (SISCOM)

This requires obtaining scans (separated by at least 48 h to accommodate radionuclide washout) during an interictal period and within seconds of seizure onset. These scans are then subtracted from one another with the use of specialized computer software. This leaves a better indication of the cortical area of ictal onset. This subtracted scan can then be co-registered onto the patient's MRI to provide support for the location of the focus [13].

2.2. Electroencephalogram (EEG) evaluation

The most useful and specific test in defining epileptogenic cortex is the EEG [14]. The approach to its utility has been discussed in the earlier sections. Features of the scalp EEG ictal discharge, other than just location, can be helpful in the presurgical evaluation. For example, it has been reported that the frequency of the initial ictal discharge in the scalp EEG correlates with the degree of hippocampal pathology in temporal lobe epilepsy [15].

Even before the clinical evaluation starts, an assessment of home videos made by a caregiver of a person living with epilepsy can give reliable information on semiological signs and help in classification of epilepsy than medical history. Agreement levels with subsequent videoEEG were seen to be 0.92 in the case of home videos as compared to 0.75 in the case of medical history [16]. Some patients may require prolonged EEG recording to note the temporal onset of seizures and interictal activity. In these patients videoEEG recordings of ictal, interictal and sleep stages and in some cases, home video EEG monitoring can also facilitate in diagnosis of epilepsy type and help in its localization to help in deciding the future course of action [16]. Magnetoencephalography (MEG) and magnetic source imaging is also being used in centers where available.

2.3. Neuropsychological testing

Routinely, all surgical candidates undergo extensive neuropsychological testing. Neuropsychologists lack consensus as to what constitutes an adequate preoperative test battery; consequently, testing is not well standardized among centers. A test battery usually contains a personality inventory (eg, Minnesota Multiphasic Personality Inventory), intelligence quotient tests, memory and language function tests, and other tests, depending on the interests of the neuropsychologist [17]. The neuropsychological testing may be tailored as per local needs (eg AIIMS battery) [18].

The earlier rationale for such testing to help localize an epileptogenic focus on the basis that subtle deficits in cognitive functioning are not so valid now with the increased availability of better imaging modalities. However, certain tests and abnormal findings have value in demonstrating lateralization of dysfunction to one hemisphere and, occasionally, to one lobe of the brain. Perhaps the best example is the testing of material-specific memory and abilities among patients with suspected temporal lobe epilepsy. In such cases, deficits in verbal memory and other verbal abilities (eg,

object naming, word list generation) are common when the seizure focus lies in the left temporal lobe in a right-handed patient. Similarly, deficits in nonverbal memory and abilities suggest right temporal lobe epilepsy in a right-handed person. These tests can also be used for other purposes, such as formulating postoperative vocational goals.

2.4. Intracarotid amobarbital (Wada) test

The intracarotid amobarbital test was initially developed by Jun Wada to preoperatively determine which hemisphere contains language function. It has also been used to test memory function within each hemisphere when considering AMTR [19].

The test is accomplished by individually cannulating each internal carotid artery. After contrast arteriography verifies that blood flows to the corresponding hemisphere and not to the brainstem or contralateral side, a dose of sodium amobarbital (sufficient to impede hemispheric function) is injected. If the drug produces a contralateral hemiparesis, function of that hemisphere is assumed to be minimized. If speech persists in the face of this hemiparesis, language function is assumed to not be represented within that hemisphere.

The deficiencies of this evaluation for memory function directly relate to the multiple problems of targeting a drug effect to specific brain structures via cerebral blood flow. Injection of a drug into the internal carotid artery does not assure drug effect in the basal temporal area in general or the hippocampal region specifically (both are areas thought to be involved in memory retrieval). This is due to variations in the direct blood supply to the hippocampus and inequalities in delivery when the drug is injected into the blood stream [20].

In addition, the test is invasive in nature. Significant complications occurred in up to 10.9% of the cases including encephalopathy (7.2%), seizures (1.2%), strokes (0.6%), transient ischemic attacks (0.6%) and localized hemorrhage at the site of catheter insertion [21]. Complications and difficulty in drug procurement in the past have led to the test being increasingly superseded by more noninvasive techniques like the fMRI [22,23]. Discordant results between the WADA test and fMRI have been noted in only 14% of the patients and occurred especially predominantly in those patients who reported either test reporting a bilateral language distribution or atypical language dominance [24]. Most centers now perform functional MRI for language and memory and thus WADA is being performed less and less.

2.5. Intracranial EEG recordings [25]

The following are examples of instances that may require invasive intracranial monitoring:

- 1) Seizures are lateralized but not localized (eg, a left-sided, widespread frontotemporal onset).
- 2) Seizures are localized but not lateralized (eg, ictal EEG patterns appearing maximally over both temporal lobes).
- 3) Seizures are neither localized nor lateralized (eg, stereotyped complex partial seizures with diffuse ictal changes or initial changes obscured by artifacts).
- 4) Seizure localization is discordant with other data (eg, EEG ictal scalp data discordant with neuroimaging [MRI, PET, SPECT] or neuropsychological data).
- 5) Relationship of seizure onset to functional tissue must be determined (eg, seizures with early involvement of language or motor function).
- 6) Relationship of seizure onset to lesion must be determined (eg, dual pathology or multiple intracranial lesions).

- 7) If seizures are clinically suspected, but video-EEG is inadequate for defining them (eg, simple partial seizures with no detectable scalp EEG ictal discharge or suspected epileptic seizures with unusual semiology that suggests psychogenic seizures [pseudo-pseudo seizures]).

It should be remembered that invasive intracranial monitoring and surgery do not result in seizure freedom in every patient.

Depth, strip, and grid electrodes are implantable intracranial devices used to record the electrocorticogram (ECoG) and to stimulate the cortex to determine function [26].

2.6. Strip electrodes

Strip electrodes are used most often to lateralize the side of seizure onset in frontal and temporal lobe epilepsy, but they may also be used to obtain survey studies over the entire cortical surface of the brain. They are usually implanted while the patient is under general anesthesia, according to the preoperative plan created by the epilepsy monitoring team. Electrodes can be directed safely over long distances within the calvaria by surfing electrodes over the brain with a gentle fluid pulse. Fluoroscopy is used to confirm placement prior to closure of the wound [27].

2.7. Subdural grid electrodes

Arrays of electrodes more than one column wide are considered intracranial grids. Practically speaking, electrode arrays that are 2–3 contacts wide cannot be easily passed for any substantial distance through a burr hole and require a craniotomy for placement. Once the decision to proceed with a craniotomy is made, grid arrays of 5–8 rows (20–64 contacts) are usually used to maximize coverage over the craniotomy site. The craniotomy site is determined based on data gathered during the presurgical evaluation; usually, a large craniotomy is performed to accommodate up to an 8 X 8-cm grid. Prophylactic antibiotics and dexamethasone are routinely administered. The grid is removed when sufficient data have been obtained to determine the site of ictal onset or, alternatively, to determine that no more recording is likely to lead to satisfactory localization [28].

If resective surgery is planned, then the relationship of the grid to the underlying cortex must stay unchanged while the craniotomy is reopened. If resection is not performed at the time of grid removal (eg, because of hemorrhage, edema, patient preference, or insufficient data), then pertinent landmarks may be documented with digital photography or frameless stereotaxy for reoperation at a later date [29].

2.8. Depth electrodes and stereo-EEG

Depth electrodes are used most commonly for recording from the hippocampus and amygdala. The approach usually preferred is via the occipital, parasagittal route. This trajectory allows for simultaneous implantation into the amygdala and anterior and posterior hippocampus using a single multi-contact electrode. Stereo-EEG has made phase II epilepsy surgery easier [30].

2.9. Staged procedures

The following are reasons a second intracranial study may be considered:

- Strip electrode survey study for lateralization and localization to a lobe, with a planned return at a later date for definition of the ictal onset zone and cortical mapping as necessary

- Reimplantation of a second grid because of failed localization secondary to sampling error (Seizures may occur on the margin of the grid, be diffuse, or show variable propagation that makes seizure localization uncertain.)
- Recurrent seizures after a previous intracranial study and resection

These procedures are typically performed months to years after the first intracranial study, either to give the wound time to heal or because seizures recur at some variable time after resective surgery.

A simple way to document the operative technique is for the monitoring team to use an anatomical brain diagram and transparencies of the grid montage to create a mock-up of the surgery. The image created is compared with fluoroscopic images taken at surgery so that a relatively accurate rendition of the electrode placement is available within minutes on the day of the surgery. These images can be quite helpful in interpreting seizure onset and propagation during EEG monitoring [31].

2.10. Cortical mapping

Often, in addition to defining the location of the epileptogenic cortex, the surgeon must determine its relationship to the functional cortex. This requires mapping the cortex underlying an implanted grid electrode. The technique is similar to that performed acutely in the operating room and requires a testing protocol appropriate to the cortical region being investigated. Cortical stimulation is performed using commercially available constant current generators. Cortical mapping is performed by selecting 2 adjacent electrodes (1 cm intervals) because bipolar stimulation provides more precise control of current flow. Bipolar pulses at 50 Hertz (Hz) are used for language, motor, and sensory mapping. Extraoperative cortical mapping has several advantages over acute intraoperative mapping. Functional mapping may be performed in multiple sessions if necessary. For example, if a seizure that impairs function is generated during mapping, the patient may be allowed to recover for several hours (or days) until proceeding with further mapping.

2.11. Complications

Published series of infection rates from all types of intracranial electrodes range from 0 to 12%. The morbidity of surgery depends on the type of electrode implantation; intracranial strip electrodes have the lowest morbidity, and intracranial grid placement has the highest morbidity.

The most common cause of morbidity in subdural strip placement is an infection. One randomized study by Wyler and co-workers found a 0.85% rate of infection between groups treated with antibiotics prior to surgery, compared with a 3% infection rate when no antibiotics were given [26]. No difference in infection rates was noted between patients who received antibiotics for the duration of strip electrode implantation versus those who received only a single preoperative dose; therefore, at the authors' institution, a single dose of antibiotics is given immediately before strip or grid implantation. Other complications of intracranial strip placement include cortical contusion, cerebral edema, brain abscess, subdural empyema and subdural hemorrhage, placement of electrodes into the brain parenchyma, accidental extraction of electrodes, and superficial wound infection. Many of these complications are minor and cause no long-term problems; permanent neurological deficit is seen in less than 1% of patients who undergo intracranial strip electrode implantation [32,33].

The rate of permanent neurological deficit from occipital depth electrode placement has been reported at less than 1%. The risk of

hitting the brainstem or posterior cerebral artery with occipitally inserted depth electrodes may be decreased by (1) targeting tip placement in the lateral amygdala and lateral hippocampus, (2) making sure the occipital burr hole is not too medial, and (3) confirming the trajectory with an image guidance system prior to electrode placement.

3. Flowchart of pre-surgical work-up in patients eligible for epilepsy surgery

The following flowchart depicts the various stages in the diagnostic algorithm of patients with drug refractory epilepsy. As we can see, imaging forms the first modality of investigation in patients with DRE following standard investigations for localization and lateralization are carried out. Patients, where even advanced non-invasive modalities are not sufficient to pinpoint the seizure focus, undergo invasive stereotactic EEG and based on those findings and patient suitability, are finally taken up for surgery or undergo other procedures [34–38].

4. Conclusion

The significance of a thorough preclinical work-up cannot be overemphasized. The choice of tests is determined by the patients' clinical profile and results. Noninvasive methods are crucial to the localization of lesions but occasionally fail in certain lesions for which invasive methods are helpful in pinpointing the seizure focus and finding a site amenable to surgery.

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Author contribution

Manjari Tripathi is incharge presurgical evaluation in AIIMS, Epilepsy Clinic, Unit III and wrote the neurological aspect of the paper. Sucharita Ray is responsible for modification of comments and manuscript during revision. Sarat P Chandra wrote the surgical aspect of the paper.

Conflicts of interest

None.

Guarantor

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