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Refractory Nonlesional Neocortical Epilepsy: Current Trends

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Abstract

Nonlesional neocortical epilepsy (NLNE) is a challenging problem to treat. Medical management with antiepileptic drugs (AEDs) frequently fails, and surgical management of refractory epilepsy is often required. With precise electrophysiological localization and resection, seizure reduction and even remission can be achieved. Frequently, lesional tissue is discovered in resected tissue specimens, even when not identified preoperatively by brain MRI. In this review, we describe the diagnostic and surgical approach to patients with NLNE refractory to medical management.

Keywords: Nonlesional neocortical epilepsy; Surgery; Focal cortical dysplasia

Introduction

Epilepsy is characterized by recurrent unprovoked seizures and has an estimated prevalence of about 5-15 per 1000 [1]. Uncontrolled epilepsy can lead to further injury of the brain and is associated with increased morbidity and mortality [2]. The etiology of epilepsy reflects a complex interaction between genetic and environmental factors that have bearing on treatment and prognosis. Approximately 25-30% of epilepsy patients do not respond to medical management with AEDs, and thus epilepsy surgery remains the most likely option for cure. Determination of potential focal epileptogenic zone (EZ) is a critical first step in management of refractory seizures. Once a potential seizure focus is identified, these patients may also be candidates for epilepsy surgery, in which precise determination and complete resection of EZs is imperative [3].

Electroencephalography (EEG) is routinely used for identification of focal ictal onset and interictal epileptiform discharges [4]. When electrophysiologic localization is concordant with neocortical lesions seen on MRI, the success of epilepsy surgery is high [5]. Even in the absence of concordant lesions on MRI, surgical resection of single foci detected by intracranial EEG (iEEG) often results in a good seizure outcome [6]. Magnetic resonance imaging (MRI) is the preferred method for initial screening of structural lesions that may represent EZs. The most well characterized lesion detected by neuroimaging is mesial temporal sclerosis (MTS) associated with temporal lobe epilepsy [7]. Less commonly, lesions of the extratemporal neocortex are revealed, which as in the case of MTS [8-12], predict a good outcome after epilepsy surgery [8`,11,13-15].

A particular challenge in the evaluation of intractable epilepsy patients is that in about 30% of extratemporal epilepsy cases, brain MRI does not identify a lesion [16]. It is increasingly recognized that in many NLNE cases, an EZ with underlying focal cortical dysplasia (FCD) may be missed by routine MRI [17,18]. Since nonlesional epilepsy is associated with a poor surgical outcome compared to lesional epilepsy, the use of multimodal imaging for localization of lesions not seen on MRI is essential to identify candidates for epilepsy surgery who are refractory to AED therapy. Indeed, multimodal imaging to localize the EZ in one study of NLNE resulted in a good seizure outcome after surgery in 80% of patients [19]. Other functional imaging modalities, including single-photon emission computed tomography (SPECT) and positron emission tomography (PET) have shown utility in evaluation and treatment of NLNE [19,20]. Magnetoencephalography (MEG) has also recently become increasingly used as an adjunct for localization of lesions. Furthermore, advances in MR image processing have allowed for improved detection of structural lesions, including FCD [21,22]. As imaging technology advances and our understanding of the pathophysiology of NLNE improves, these cases should become more effectively managed. In this review, we will discuss recent work related to the pathophysiology of NLNE and the diagnostic and surgical approaches to management of this disease.

Neuropathology in Neocortical Epilepsy: Does Nonlesional Neocortical Epilepsy Exist?

In most cases of neocortical epilepsy, intracranial EEG (iEEG) monitoring will be necessary to localize the seizure focus often in conjunction with structural abnormalities detected by brain MRI [23]. The detection of a structural lesion i.e., tumor, vascular malformation, or FCD, assuredly aids with localization of the resection site and in fact, there is often, though not exclusively, close correlation between the lesion location and seizure focus. From a clinical perspective, co-localization of an anatomic lesion and the seizure focus determined by intracranial electrodes can predict a more successful seizure free outcome. This makes intuitive sense since the lesion is conceptually thought to cause seizures by virtue of the disruption of tissue architecture. The resection of an epileptogenic lesion within an ictal onset zone (IOZ) is recognized as among the most important factors linked to a favorable surgical outcome [3]. The majority of surgical series have suggested that the presence of a specific lesion usually leads to a favorable surgical outcome [24]. The presence of a lesion increases the likelihood of seizure freedom and thus, brain MRI is relatively good at predicting the prognosis of neocortical epilepsy. In contrast, if no lesion is seen on pre-operative MRI, this suggests a diagnosis of NLNE. An important reason for an unfavorable operative outcome in patients with NLNE is the inherent difficulty of identifying the EZ [25]. However, recent studies have shown that the presence of a lesion

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may not necessarily predict a more favorable surgical outcome and that resection of radiographically normal appearing tissue may afford a successful outcome [26]. This finding may reflect that the electrical IOZ extends beyond the anatomical extent of the brain lesion or that the anatomic extent of the lesion is unappreciated radiographically.

Surgical resection will yield tissue for neuropathological analysis that may provide a definitive diagnosis. Neuropathologists use several approaches to classify the tissue pathology including immunohistochemistry to define proteins such as neurofilaments, glial fibrillary acidic protein, and markers of cell division or inflammation. Many resected areas will exhibit a clear pathological abnormality such as FCD, low-grade tumors, vascular malformation (e.g., AVM), hypoxic-ischemic damage, or gliosis [27]. In one study of 62 frontal lobe epilepsy patents, 46 exhibited FCD [27]. The histopathological features of FCD have been classified [28,29]. Type IA and IB exhibit a more mild disruption of cortical cytoarchitecture. For example, FCDIA or IB, laminar architecture is relatively preserved whereas in FCDIIA and FCDIIB there is a complete loss of lamination. FCDIIA is characterized by disorganized cortical lamination and the presence of enlarged and dysmorphic neurons. FCDIIB is characterized by cortical laminar disorganization, dysmorphic neurons, and balloon cells (BCs). Tumors include low-grade glioma, ganglioglioma, or oligodendroglioma. Ganglioglioma and dysembryoblastic neuroepithelial tumors (DNET), low grade neoplasms that are closely linked to dysplasias, are among the most common low-grade neoplasm identified in intractable pediatric epilepsy patients. These tumors exhibit mixed histopathological features including proliferative astrocytes, dysmorphic neurons, and large cells of unclear cellular lineage known as atypical ganglion cells. Small areas of hypoxic-ischemic injury and encephalomalacia may be seen and occur by unknown mechanisms. The clinical significance of gliosis is also unknown but could reflect an early *in utero* hypoxic-ischemic injury or viral infection. For each of these lesion subtypes, the current belief is that epileptogenesis results from cellular abnormalities i.e., changes in cell structure or type, alterations in the expression of neurotransmitter receptor subunits or ion channels, or the effects of inflammatory cells such as microglia that are typically seen in these lesions. Electrophysiological analyses of acute slices from FCD specimens have demonstrated that cytomegalic pyramidal neurons in FCD have larger membrane capacitance, time constant, and input resistance than normal-appearing pyramidal neurons [30]. Cytomegalic pyramidal neurons display repetitive calcium oscillations, a sign of hyperexcitability. Interestingly, BCs are relatively electrically silent. One observation has been that all of these lesion types exhibit abundant numbers of astrocytes that may also contribute to epileptogenesis by altering ambient levels of glutamate, an excitatory neurotransmitter.

A more vexing clinical problem is when no lesion is seen on brain MRI that coincides with the predicted IOZ identified by scalp EEG. In these so-called "nonlesional" cases, MRI at 3Tesla strength does not visualize a lesion that could be causative for recurrent seizures. Thus, the tacit assumption is either that there is no lesion in the brain or that the lesion is below the level of MRI resolution. For example, among 89 intractable epilepsy patients with normal brain MRI, fully 58 had evidence of tissue pathology [19]. Indeed, in most the NLNE cases, histopathological analysis reveals microscopic changes suggesting lesional pathology and demonstrating that most NLNE cases are actually lesional cases. In tuberous sclerosis complex, while tubers are typically visualized by brain MRI, there may be extensive micropathology beyond tubers alone such as focal heterotopias, isolated abnormal cell types, and areas of subtle cortical dyslamination [31]. As in the case of lesional resections, when pathological changes are identified in NLNE cases, the usual diagnoses include FCD or gliosis. It is unusual for NLNE to result from a low-grade neoplasm and uncommon for the pathology to reveal a high-grade neoplasm. On rare occasions, no pathological changes are identified but this finding is entirely dependent on the extent of pathological investigation. Unless a careful analysis of the tissue specimen is undertaken, it is possible that subtle FCD e.g., type IA, can be missed. In the case of truly normal brain architecture within the resected region, the mechanisms of epileptogenesis remain a mystery.

Seizure Semiology and Pre-surgical Clinical Evaluation

The objective of pre-surgical evaluation is to determine the location and extent of the EZ and its relationship to eloquent cortex. This can be a challenging task in nonlesional epilepsy particularly due to the difficulty in demarcating the extent/margins of the EZ. The currently accepted approach includes the accumulation of information based on history, exam, neuropsychological testing, WADA, multimodal imaging, and phase 1 video-EEG monitoring to confirm diagnosis and capture interictal and ictal scalp EEG activity along with ictal semiology. In the best case scenario, this information should all concordantly point to the same EZ. In the case of NLNE, the patients almost always require phase 2 video-EEG monitoring with iEEG. The phase 1 information, however, is crucial in deciding the extent and type of intracranial electrodes used. As part of phase 2 of the pre-surgical evaluation, the interictal and ictal iEEG pattern will aid in demarcating the extent of the EZ and mapping eloquent cortex.

It is essential to obtain a detailed description of all seizure types and behaviors as they may be the first indication of solitary versus multifocal disease. Specific details such as description of an aura can be the first key to localizing or lateralizing the EZ. At the same time, a thorough physical exam with careful attention to subtle weakness, sensory loss, or a skin lesion may be helpful in finding a previously unknown underlying disease or provide clues about the localization of the lesion.

The neuropsychological assessment may reveal areas of dysfunctional cortex which may help localize the lesion in NLNE. Additionally a lower IQ may suggest a poor prognosis as it may be a surrogate to a more generalized or multifocal disease [32]. The major benefit of both neuropsychological testing and WADA is to understand the potential risk of cognitive deficits after surgery and educate the patient and family prior to resection.

Inpatient video-EEG monitoring occurs in a supervised semi-controlled environment with trained personnel with the goal of capturing all seizure types. It can be helpful in clarifying the disease and most notably localizing and lateralizing the EZ. The seizure semiology can be seen on video and scrutinized for localizing and lateralizing signs. It stands to reason that the seizure semiology represents the cortical discharge in a specific region and provides clues as to the symptomatogenic zone. However, seizures can spread rapidly, and behavior caused by the spread of the seizure can present as a false localizing sign. Careful attention to the order of the event and clearly stereotyped events may provide reassurance about the reliability of a single focus of disease. Table 1 gives examples of localizing and lateralizing clinical semiology based on the area of cortex involved [33-40]. This can be paired with ictal and postictal lateralizing features, which together will give a better sense of the EZ involved [40]. The main contribution of the semiology is to aid in placement of the intracranial electrodes, but the semiology itself does not appear to determine the clinical outcome [41].

Epileptogenic zone		Semiology
Temporal	Medial Temporal lobe	• Déjà vu, fear, viscero-sensory auras with nausea, rising epigastric sensation • Staring and limited motor movement with oral or manual automatism • Autonomic features • Dystonic posturing contralateral to seizure focus with ipsilateral automatism • Ictal speech, vomiting may suggest a non-dominant lateralization • Postictal aphasia suggests dominant lateralization
	Neocortical temporal lobe	• Aura of auditory phenomena, déjà vu, complex visual distortions, vertigo • Motionless staring and unresponsiveness • Contralateral clonic movements
Frontal	Mesial frontal	• Ictal fear • Ictal laughter without mirth • Onset in sleep • Fencing posture • M2e posture (contralateral shoulder abduction, elbow flexion, head deviation toward affected arm) • Figure-of-4 posture • Hyperkinetic seizures including body rocking, kicking or boxing
	Dorsolateral frontal	• Spreading clonic activity • Versive seizures • Lateral eye deviation • Aphasia • Nocturnal hypermotor activity • Laughing, shouting, bicycle peddling, thrashing of extremities
	Orbitofrontal	• Hypermotor automatisms • Thrashing movements • Sudden motion arrest, unresponsiveness, staring
	Insular	• Laryngeal discomfort • Sensation of throat constriction followed by contralateral paresthesias
Parietal		• Auras of contralateral tingling, numbness, pain, thermal sensation • Motor activity depending on spread to sensorimotor temporolimbic, supplemetary motor or premotor cortex
Occipital		• Contralateral simple visual distortions, blindness • Ocular pain • Tonic deviation, nystagmus, eyelid fluttering

Table 1: Common examples of localizing and lateralizing semiology [60-67].

Electrophysiology and Multimodal Imaging

Multimodal imaging is critical for evaluation of NLNE, although approaches to combining modalities are highly variable and dependent on the clinical context of each case. Intracranial EEG is the gold standard for IOZ localization but carries increased risk compared to non-invasive imaging methods. The use of multimodal non-invasive imaging may improve EZ localization, allow for smaller resections during epilepsy surgery, guide placement of iEEG electrodes, and in some cases prevent the need for a lengthy and invasive iEEG evaluation altogether.

Scalp EEG is always performed during evaluation of NLNE. Interictal scalp EEG predicts both ictal onset localization and good surgical outcome in NLNE when spikes remain strictly localized to a single area [42]. This is uncommon in NLNE and more frequently scalp EEG reveals multifocal or mislocalized EZs, such as in putative neocortical temporal epilepsy [43]. Recent studies have revealed more subtle EEG findings associated with favorable outcomes of epilepsy surgery, such as ictal onset focal beta discharges on both scalp EEG and iEEG [44]. High frequency oscillations at >80 Hz on iEEG have been associated with IOZs, and thus may have value in evaluation of NLNE [45]. Additionally, ictal onset baseline shifts and infraslow activity at <0.1 Hz has been shown to have localizing value in focal epilepsies [46].

PET and subtraction ictal SPECT studies have been used for many years to assist in localization of EZs, which are often hypometabolic on interictal PET and show increased ictal and decreased interictal regional perfusion by SPECT [47,48]. Direct comparison between MRI, FDG-PET, and subtraction ictal SPECT localization in neocortical epilepsy has shown variable sensitivity depending on the type of lesion, with higher sensitivity of PET and MRI compared to SPECT for tumor localization and higher sensitivity of PET and SPECT compared to MRI for neuronal migration disorders [49]. In the 30% of patients with normal MRI in one study, PET and SPECT imaging produced correct localization of lesions in 60% and 55% of cases as confirmed by pathology [49]. The use of PET/MRI coregistration has also shown utility in improving detection of lesions i.e., FCD, tumor, AVM, and can guide repeat MRI analysis to improve lesion detection [50,51]. However, traditional PET and subtraction ictal SPECT imaging generally show unimpressive concordance with iEEG in NLNE, showing value in EZ localization in about half of patients [43].

Analysis of subtraction ictal SPECT alone may fail to identify focal changes due to variability in uptake patterns. Furthermore, small differences between ictal and interictal SPECT and variability in overall intensity and orientation make visual side by side interpretation of EZs difficult. Subtraction ictal SPECT coregistered with MRI (SISCOM) largely solves these problems, and compared to subtraction ictal SPECT and FDG-PET, SISCOM shows better concordance with iEEG, particularly for extratemporal epilepsy [52-55]. EZ localization by SISCOM has been shown to predict a favorable outcome of epilepsy surgery [52-54,56]. It is important to note that localizability in these studies were dependent in part on early radiotracer injection times [43,52]. In cases requiring iEEG, SISCOM has been shown to improve placement of the electrodes, and even in patients who have failed previous epilepsy surgery, SISCOM may be useful for evaluation of repeat surgery [56,57].

The contribution of MEG to surgical evaluation of both lesional epilepsy and NLNE is well established [58-63]. MEG often shows high concordance with iEEG, similar to that of SISCOM, and concordance between MEG and iEEG with normal MRI is associated with better

outcomes of epilepsy surgery [55,64-66]. When MEG reveals a single cluster of dipoles within the resected IOZ, the seizure outcome is very good, compared to poorer outcomes with multiple dipole clusters [65,67]. In addition to improving placement of intracranial electrodes, MEG can prompt re-evaluation of "normal" MRI to improve detection of structural lesions, potentially preventing the need for iEEG [61,62,66,68].

These imaging studies demonstrate our increasing ability to specify EZs in NLNE. Newer imaging modalities, including diffusion tensor imaging and functional MRI, will likely gain increasing use in the near future for preoperative evaluation in this challenging type of epilepsy [69,70]. When any of the imaging modalities reveal concordant localization the outcome is usually good, however when discordant, invasive approaches become necessary and outcomes are generally poor. Clinical management becomes especially difficult if iEEG confirms multiple IOZs.

Surgical Considerations in Extratemporal Epilepsy

Surgery is a late consideration in the treatment of NLNE. As we have described, where medical treatment fails and a localizable lesion is identified, resective surgery may be considered. As shown in table 2, numerous other surgical approaches may have merit, particularly some of the stimulative approaches. The spatial and temporal resolution of long term scalp EEG is limited. Therefore, a question may arise whether there is a bilateral focus or a unilateral focus with rapid generalization. Second, when the side is known, high resolution invasive localization is often necessary in the form of a large lobar grid.

Invasive electroencephalography

Invasive EEG monitoring is necessary for cortical resection when the epileptic focus is not clear. Subdural strip electrodes are used primarily to lateralize an epileptogenic focus, and large subdural grids are used to unilaterally localize a focus. It is important to cover as much of the suspected area as possible for accurate lateralization and localization [71]. In our center, we routinely identify electrode locations in image space by coregistering postoperative MRI and CT images. If the electrodes are properly indexed in the image, an electroradiographic record of the eloquent and epileptogenic regions can be obtained and used as a navigational tool during resection. Subdural strip electrodes are placed through a bur hole and passed blindly into the subdural space. Multiple electrodes may be inserted through one bur hole to cover wide regions of the brain. In patients with bifrontal discharges, strip electrodes are placed over the medial and lateral surfaces of the posterior frontal lobe from bur holes at the coronal suture, just off the midline [72]. Subdural grid electrodes are placed with a craniotomy. They are used primarily for determining the site of seizure onset over the convexity of one hemisphere. They can also be used for extraoperative functional mapping by knockout stimulation of each electrode. The maximal extent of an epileptogenic focus and areas of cortical function are determined with these evaluation methods [73]. With invasive EEG methods, the electrode leads are brought out through the scalp and the patient is monitored for many days. The most common complications are infection and leakage of cerebrospinal fluid, especially with a large subdural grid.

Resection
Hemispherectomy: resection of the cerebral hemisphere Lobectomy: resection of one cerebral lobe Topectomy: resection of a focal area of cerebral cortex
Disconnection
Corpus callosotomy: disconnection of two hemispheres Multiple subpial transection: disconnection of a focal area of cerebral cortex Hemispherectomy: Disconnection of a cerebral hemisphere
Stimulation
Vagal nerve stimulation Anterior thalamic stimulation Responsive neurostimulation

Table 2: General categories of epilepsy surgery.

Anatomy

The extent of cortical resection is based on the results of presurgical evaluation and findings on intraoperative recording and stimulation. Resection of essential cortex such as the language and precentral arm or leg motor cortex should be absolutely avoided in adults because of the resultant hemiparesis or aphasia. Therefore, it is particularly important to identify language and motor cortical sites before proceeding with resection surgery. Anatomically, the frontal lobe Broca speech area is identified in the opercular, inferior frontal gyrus (usually the posterior 2.5 cm of this gyrus). It is difficult to identify Wernicke's area by anatomic criteria. The parietal speech area is identified 1 to 4 cm above the sylvian fissure and 2 to 4 cm behind the postcentral sulcus. The temporal speech areas usually extend posteriorly behind the level of the postcentral sulcus and 2 to 3 cm from the adjacent convolution above, behind Heschl's gyri. Lack of defining anatomic features for Wernicke's area renders language mapping essential for cortical dominant hemisphere resections [74]. Large frontal resections in the nondominant hemisphere may be carried out in front of the precentral gyrus. Rough localization of the precentral and postcentral gyri is performed by identifying the somatosensory evoked potential (SSEP) phase reversal over the central sulcus [75]. Subsequently, identification of the precentral and postcentral gyri is accomplished by stimulation under anesthesia without neuromuscular blockade [73]. Some surgeons prefer an awake patient for motor mapping. Resection of precentral arm or leg motor cortex is permitted only if significant contralateral paresis is already present [75]. The lower nondominant precentral face area can be resected as long as the resection does not extend into the underlying white matter. The resulting contralateral facial paresis improves but may not return to normal [76]. Resection of the postcentral sensory arm or leg area causes a profound proprioceptive deficit and is rarely indicated, although improvement over a period of several months is possible. In the nondominant hemisphere, the entire parietal cortex posterior to the postcentral gyrus can be removed without inducing a sensorimotor deficit. Resection in the parietal operculum may produce contralateral lower quadrantic hemianopia if resections are carried beyond the depths of the sulci into the white matter. In the dominant hemisphere, parietal lobe resections should be limited to the superior parietal lobule. Language functions are subserved by cortex of the inferior parietal lobule, and a disabling Gerstmann syndrome can also result from extensive parietal lobe resection. Large resections of occipital cortex produce a contralateral homonymous hemianopia. Therefore, if vision is intact preoperatively, the calcarine cortex and optic radiations are spared as much as possible. Because cortex essential for reading is often more widespread than that for naming, excision within 2 cm of Wernicke's area may cause a persisting dyslexia. The vascular territory of each cortical artery or vein should be studied to assess the consequences of occlusion of the vessel during surgery. This approach is essential to minimize morbidity, especially with surgery on the motor and speech areas. Any ascending vein to the superior sagittal sinus draining from the central or postcentral sulci should be left intact to avoid significant morbidity.

Preoperative care and anesthesia

It is our practice to reduce the doses of antiepileptic medications

the week before surgery so that the epileptogenic cortex is as active as possible during surgery [77]. Some epilepsy centers do not use this strategy, particularly in situations in which they will be carrying out awake craniotomies. When resecting noneloquent cortical areas, general anesthesia can be used [76]. However, when intraoperative electrocorticography (ECoG) is required, the use of drugs that depress cortical electrical activity, such as benzodiazepines and barbiturates, should be avoided. In addition, when functional mapping of speech and sensory areas is performed, the patient should be conscious and cooperative during the procedure. In this situation, local and total intravenous anesthesia with analgesic drugs (fentanyl and droperidol or propofol) should be used [78]. Local anesthesia alone has the disadvantages of taking more time to create a complete block and limiting the range of head positions that can be used. Furthermore, it cannot be used with uncooperative patients and young children. Constant supervision by a specially trained anesthesia team is essential [76].

Intraoperative electrocorticography

Sufficient brain exposure via craniotomy is essential during ECoG. ECoG is performed to further delineate the extent of the EZ. The intention is to identify regions with primary epileptic neurons by identifying brain sites that have interictal ECoG spikes. In our experience, there is a clear relationship among the site of interictal discharges, the site of ictal onset, and the tissue that must be removed to control seizures. This ECoG hallmark is used to determine what part of the brain should be resected [72,73,78]. ECoG also provides prognostic information by indicating areas with residual discharges after cortical resection. Patients with no interictal discharges on postresection recordings are more likely to be free of seizures than those with persisting discharges [73-79]. For "standard" temporal lobectomy surgery, the value of ECoG is not as clear.

Cortical stimulation (Functional mapping)

The purpose of intraoperative cortical stimulation is to localize eloquent cortex such as the motor cortex, sensory cortex, or language area in the dominant hemisphere. Functional mapping is necessary when cortical resections are carried out near eloquent brain areas. Identification of motor cortex is useful for any resection in the posterior frontal or parietal lobes. Identification of language cortex is necessary for any dominant-hemisphere resection in the perisylvian cortex and posterior superior frontal lobe. The location of the central sulcus is determined by electrical stimulation of the precentral and postcentral gyri after preliminary identification by monitoring for the SSEP phase reversal. The suspected site of the motor and sensory cortex is stimulated and mapped with a motor response detected by the anesthetist, measurement by electromyographic electrodes, or a report of sensory change by the patient [79]. In practice, the best way to identify the postcentral gyrus is to induce sensory responses in the tongue area located at the bottom of the postcentral gyrus [80]. The frontal, parietal, and temporal language areas in the dominant hemisphere are stimulated while the patient carries out simple verbal tasks such as naming objects shown on picture cards. A language critical area is identified if the patient is unable to speak (speech arrest) when the site is being stimulated or if the patient can speak but is unable to name objects [75]. Although failure to produce speech arrest or anomia does not always exclude the presence of language critical sites in the stimulated cortex, intraoperative mapping is nevertheless the most reliable method currently available for identifying these language critical sites.

Resection technique

Unlike temporal lobectomy, there are no anatomically standard operations for extratemporal cortical resection. A craniotomy is performed to expose the epileptic focus that will be resected. The extent of neocortical resection is based on the gross pathology and the results of ECoG and functional mapping. In general, effort is made to resect all areas with interictal discharges. Essential motor and language areas should be preserved (preferably with a 2 or 1 cm margin), regardless of involvement in the epileptic focus. Special attention is also given to the vascular supply of the area to be resected. The extent of the resection is individually tailored to each case. Meticulous, slow removal of epileptogenic gray matter is carried to the bottom of the sulcus without damaging vessels within the pia that might supply other nonresected tissue. Hemostasis is achieved principally with topical agents such as Gelfoam or Surgicel and minimal use of electrocautery. With the topectomy procedure, unnecessary resection of the underlying white matter is avoided to preserve the integrity of projection, association, and commissural fibers. Appropriate antiepileptic medication and dexamethasone are administered after cortical resection.

Outcome

Extratemporal nonlesional resection is associated with worse seizure control rates and a higher incidence of major postoperative morbidity than lesional or temporal lobe resection surgery. Extratemporal surgery results in seizure-free rates of 45% and improvement in 35%. More recent work shows comparable results. With localized resective surgery, less than 5% of patients have some postoperative neurological deficit as a result of unintended vascular compromise or other accidental damage to essential neural tissue (Table 3). Most of these deficits are transient and resolve within months, however. Postoperative bleeding and infection are uncommon. Seizures in the acute postoperative period may portend a poor prognosis, and most patients will continue to require pharmacologic treatment.

Vagal nerve stimulation

Vagal nerve stimulation (VNS) was approved in 1997 for patients over 12 years old with partial onset seizures refractory to drugs. There has not been a specific survey of VNS for NLNE. However, medically refractory partial onset seizures are typically the seizure type for NLNE. On average, VNS delivers a 34% seizure reduction at three months, and 45% reduction in seizure frequency at 12 months following implantation. 20% had greater than 75% seizure reduction and 2% of patients become seizure free with VNS. Adverse effects include hoarseness, dysphagia, coughing and perception of the stimulation. Overall, it is a safe procedure with low morbidity, but not as effective as resection. It may be used as an adjunct to medication or after resective surgery. One unique feature of the VNS is the magnet current. If a patient has an aura, he or she can swipe a wearable permanent magnet across the generator under the clavicle and instant stimulation current is delivered which can sometimes abort a seizure.

Seizure Outcome	ATL (%)	ETR (%)
Seizure Free	2429 (67.9)	363(45.1)
Improved	860 (24.0)	283 (35.2)
Not Improved	290 (8.1)	159 (19.8)
Total	3579 (100)	805 (100)

ATL: Anterior Temporal Lobectomy; ETR: Extratemporal Resection

Table 3: Outcome of temporal and extratemporal seizures [76].

Deep brain stimulation

Deep brain stimulation of the anterior nucleus of the thalamus is not FDA approved, but may have some utility in treating NLNE instead of or in addition to surgical resection. The results were initially published in 2010, and showed an approximately 50% reduction in seizure frequency among study participants in 3 month follow up [81]. Recent data showed a 70% reduction in seizure frequency after 5 years. The device is approved in the EU and Canada, but awaits FDA approval in the United States.

Conclusion

NLNE encompasses a broad range of clinical and pathological diagnoses and is associated with greater difficulty in identifying a discrete seizure focus than neocortical epilepsy associated with a lesion. While there is no "best" diagnostic approach, the overarching treatment principle is to localize the epileptic zone as accurately as possible by multimodal imaging and iEEG to offer a surgical resection with little neurological morbidity. Indeed, every operation is customized to each individual patient. NLNE surgery requires a more extensive and invasive preoperative diagnostic evaluation than temporal lobectomy, and the probability of a seizure free e.g., Class I, outcome is lower with this type of epilepsy surgery than with temporal lobe epilepsy. Nevertheless, topectomy can decrease and sometimes eliminate disabling epilepsy at a reasonable neuropsychological cost. Because NLNE seems to afflict a much larger volume of tissue in a network fashion, stimulative approaches such as VNS and DBS may have primary or adjuvant utility.

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