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Minireview

Surgical treatment for epilepsy

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Abstract

Nearly one-third of patients with newly diagnosed epilepsy will develop medically refractory seizure disorders. The initial response to antiepileptic drug therapy is highly predictive of long-term outcome. Patients with intractable epilepsy may have a progressive disorder that is medically, physically, and socially disabling. Surgical resection of the epileptogenic zone or lesional pathology, or both, may significantly reduce seizure tendency in selected patients. The present review supports the position that early and effective epilepsy surgery may not only render the patient with intractable partial epilepsy seizure-free, but also allow the individual to become a participating and productive member of society. Patients with surgically remediable epileptic syndromes should be identified early in the evaluation and treatment of their seizure disorders. Favorable candidates for focal cortical resection include individuals with medial temporal lobe epilepsy and partial seizures related to selected lesional pathology, e.g. primary brain tumor or vascular anomalies. In conclusion, surgical treatment of intractable partial epilepsy has been shown to compare favorably to antiepileptic drug therapy. Individuals rendered seizure-free may experience a significant improvement in quality of life. Patients who fail to respond to initial antiepileptic drug therapy should be "triaged" to a presurgical evaluation. Ictal semiology combined with structural magnetic resonance imaging and the electroclinical correlation may permit identification of candidates for early and effective surgical treatment.

Keywords: Epilepsy surgery; Intractable epilepsy

1. Introduction

Partial or localization-related epilepsy is the most common seizure disorder (Dreifuss, 1987; Cascino, 1996; Mattson, 1992). The most frequently occurring seizure-type in the adult patient is a complex partial seizure of mesial temporal lobe origin (Dreifuss, 1987; Cascino, 1996; Mattson, 1992). Approximately, 45% of patients with partial epilepsy will experience medically refractory seizures that are physically and socially disabling (Dreifuss, 1987). A minority of patients who fail to respond to first-line antiepileptic drug therapy will be rendered seizure-free with newer medical treatments introduced in the past decade (Camfield and Camfield, 1996; Hauser and Hesdorffer, 1990; Hauser,

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1992). Epilepsy surgery is an effective alternative form of therapy for selected patients with intractable partial epilepsy (Dreifuss, 1987; Cascino, 1996; Radhakrishnan et al., 1998; Van Buren et al., 1975; Crandall, 1987; Cascino et al., 1993a; Awad et al., 1991; Engel and Ojemann, 1993). Patients with medial temporal lobe epilepsy and lesional epilepsy may be favorable candidates for epilepsy surgery and have a surgically remediable epileptic syndrome (Cascino et al., 1993a; Cascino, 1996). The majority of these patients experience a significant reduction in seizure tendency following surgical ablation of the epileptic brain tissue (Awad et al., 1991; Cambier et al., 2001; Cascino et al., 1993b, 1996; Crandall, 1987; Engel and Ojemann, 1993; Mosewich et al., 2000; Radhakrishnan et al., 1998; Van Buren et al., 1975). The hallmark pathology of medial temporal lobe epilepsy is mesial temporal sclerosis (Cambier et al., 2001; Cascino et al., 1992, 1993b; Jackson, 1996). The surgically excised hippocampus in these patients almost invariably shows focal cell loss and gliosis (Cambier et al., 2001; Cascino et al., 1992, 1993b, 1996; Jackson, 1996). Patients with lesional epilepsy may have a primary brain tumor, vascular anomaly or a malformation of cortical development (MCD) (Awad et al., 1991; Cascino et al., 1992, 1993a,b; Mosewich et al., 2000). The common surgical pathologies encountered in patients with lesional epilepsy include a low-grade glial neoplasm, cavernous hemangioma and focal cortical dysplasia (Cascino et al., 1993a; Awad et al., 1991). Individuals with mesial temporal sclerosis and lesional pathology almost invariably have an abnormal structural magnetic resonance imaging (MRI) study and the seizure-types are classified as substrate-directed partial epilepsy (Cascino et al., 1992, 1993a; Cascino, 1996, 2001; Palmini et al., 1991). The MRI in these individuals may detect a specific intra-axial structural abnormality that may suggest the likely site of seizure onset and the surgical pathology (Cascino, 2001). MRI has a pivotal role in the selection and evaluation of patients for alternative forms of therapy (Cambier et al., 2001; Cascino et al., 1993a,b, 1996; Jackson, 1996; Radhakrishnan et al., 1998). The rationale for the presurgical evaluation is to identify the site of ictal onset and initial seizure propagation, i.e. epileptogenic zone, and determine the likely pathological findings underlying the epileptic brain tissue (Engel and Ojemann, 1993; Cascino et al., 1996). In patients with an MRI-identified foreign-tissue lesion or unilateral mesial temporal sclerosis the purpose of the electroclinical correlation is essentially to confirm the epileptogenicity of the structural abnormality (Cascino et al., 1992, 1996; Mosewich et al., 2000). The demonstration of concordance between the pathological substrate and the ictal onset zone indicates a highly favorable operative outcome in selected individuals. Approximately 80% of patients with unilateral mesial temporal sclerosis, a low-grade glial neoplasm, or a cavernous hemangioma are rendered seizure-free following surgical treatment (Awad et al., 1991; Cambier et al., 2001; Cascino et al., 1992, 1993b; 1996; Cascino, 1996; Mosewich et al., 2000; Radhakrishnan et al., 1998). Over 90% of patients with these pathological findings will experience an excellent surgical outcome, i.e. auras only or rare non-disabling seizures (Radhakrishnan et al., 1998). The operative outcome is distinctly less favorable in individuals with focal cortical dysplasia and other MCDs (Palmini et al., 1991). The most common operative strategy in patients with intractable partial epilepsy involves a focal cortical resection of the epileptogenic zone with an excision of the surgical pathology (Awad et al., 1991; Cascino et al., 1993a). The goals of surgical treatment are to render the individual seizure-free and allow the patient to become a participating and productive member of society (Cascino, 1996; Crandall, 1987; Dreifuss, 1987).

2. Non-substrate-directed partial epilepsy

The seizure-types in patients with localization-related seizure disorders and normal MRI studies are classified as non-substrate-directed partial epilepsy (Cascino, 2001). The anatomical localization of the epileptogenic zone in these individuals commonly involves the neocortex, i.e. extrahippocampal areas (Cascino et al., 1992; Cascino, 2001). The most frequent site of seizure onset in patients with neocortical non-lesional partial epilepsy is the frontal lobe (Cascino et al., 1992; Mosewich et al., 2000). The surgical pathology in these patients includes gliosis, focal cell loss, MCD, or no histopathological alteration (Cascino et al., 1992). The MRI may rarely be indeterminate in selected lesional pathology, e.g. focal cortical dysplasia (Cascino, 2001). Only a minority of patients with neocortical, extratemporal seizures are rendered seizure-free following surgical treatment (Cascino et al., 1992; Cascino, 2001). An estimated 20–30% of these patients with extratemporal, mainly frontal lobe, seizures will enter a seizure remission following a focal cortical resection (Cascino et al., 1992). An important reason for the unfavorable operative outcome in patients with non-substrate-directed partial epilepsy is the inherent difficulty identifying the epileptogenic zone (Cascino et al., 1992). The potential limitations of interictal and ictal extracranial and intracranial EEG monitoring in patients with partial seizures of extratemporal origin have been well-defined (Cascino et al., 1992). The anatomical region of seizure onset may represent a continuum in these patients that lends itself to an incomplete focal resection of the epileptogenic zone. A large resection increases the likelihood of rendering the patient seizure-free, but it also increases the potential for operative morbidity (Cascino et al., 1992; Cascino, 2001). Advances in peri-ictal imaging (see below) have assisted the selection of operative candidates with non-substrate-directed partial epilepsy, altered the preoperative evaluation, and tailored the surgical excision (Henry et al., 1994; Henry, 1996; Ho et al., 1995; O'Brien et al., 1996; Spencer, 1994; Theodore, 1996).

3. Neuroimaging in non-substrate-directed partial epilepsy

Neuroimaging studies used to localize the epileptogenic zone in patients with non-substrate-directed partial epilepsy being considered for surgical treatment include positron emission tomography (PET), magnetic resonance spectroscopy (MRS), and single photon emission tomography (SPECT) (Cendes et al., 1997; Henry et al., 1994; Henry, 1996; Ho et al., 1995; O'Brien et al., 1996; Spencer, 1994; Theodore, 1996; Kuzniecky et al., 1998). These imaging modalities may be of particular importance in the individuals with an indeterminate structural MRI and presumed extratemporal seizures. The emergence of peri-ictal functional imaging techniques co-registered with structural MRI have assisted identification of potential operative candidates and altered surgical strategy.

3.1. Single photon emission computed tomography

SPECT is most appropriate for peri-ictal imaging in patients with partial epileptic syndromes being considered for epilepsy surgery (Brinkmann et al., 2000; Fessler et al., 2000; Ho et al., 1995; Marks et al., 1992; Newton and Berkovic, 1996; O'Brien et al., 1996, 1998a,b, 1999a,b, 2000; So, 2000; So et al., 2000). There is a broad consensus that ictal SPECT studies are superior to interictal images in localization-related epilepsy (Ho et al., 1995; Marks et al., 1992; Newton and Berkovic, 1996). SPECT studies involve cerebral blood flow imaging using radiopharmaceuticals that have a rapid first pass brain extraction with maximum uptake being achieved within 30–60 s of an intravenous injection (Marks et al., 1992; Newton and Berkovic, 1996; O'Brien et al., 1999a). The SPECT images can be acquired up to 4 h after the termination of the seizure so that the individual patient can recover from the ictus prior to being transported to the nuclear medicine laboratory. SPECT studies have an important clinical application in the potential identification of the epileptic brain tissue when the remainder of the non-invasive presurgical evaluation is unable to lateralize or localize the site of seizure onset (O'Brien et al., 1998a).

The initial blood flow SPECT studies in patients with intractable partial epilepsy involved interictal imaging which variably detected a focal hypoperfusion in the region of the epileptogenic zone (Spencer, 1994). Interictal SPECT images have proven to have a relatively low sensitivity and a relatively high false positive rate in temporal lobe epilepsy (Spencer, 1994). Interictal SPECT also been shown that to have a low diagnostic yield in patients with extratemporal seizures (Ho et al., 1995). Ictal SPECT studies have been confirmed to be useful in patients with temporal lobe epilepsy to identify a region of focal hyperperfusion (Ho et al., 1995). The rationale for interictal SPECT imaging at present is to serve as a reference for a baseline study for the interpretation of ictal SPECT images. The diagnostic yield of ictal SPECT has been established to be superior to interictal SPECT in patients being considered for surgical ablation procedures. The recent development of stabilized radiotracers that do not require mixing immediately before injection, such as ^{99m}Tc-bicisate, has made ictal SPECT more practical in patients with extratemporal seizures that often are not associated with an aura and may have a shorter seizure duration (O'Brien et al., 1999a). Unfortunately, ictal SPECT has a poorer spatial resolution than PET (Spencer, 1994).

3.2. SISCOM

The imaging paradigm using computer-aided subtraction ictal single photon emission tomography (SPECT) co-registered to MRI (SISCOM) has been introduced in patients with intractable partial epilepsy (Brinkmann et al., 2000; Fessler et al., 2000; O'Brien et al., 1996, 1998a,b, 1999a,b, 2000; So, 2000; So et al., 2000). Subtracting normalized and co-registered ictal and interictal SPECT images, and then matching the resultant difference image to the high resolution MRI for anatomical correlation has been shown to be a reliable indicator of the localization of the epileptogenic zone in patients with localization-related epilepsy (Brinkmann et al., 2000; O'Brien et al., 1998b, 1999b; So, 2000). The technique used at Mayo Clinic has compared favorably to the traditional visual analysis of the interictal and ictal images. SISCOM in a series of 51 patients had a higher rate of localization (88.2% versus 39.2%, $P < 0.0001$), better inter-observer agreement, and be a better predictor of surgical outcome than visual inspection of the interictal and ictal images (O'Brien et al., 1998a). The study demonstrated the inherent problems with visual interpretation of either peri-ictal or interictal SPECT studies alone.

The methodology used for SISCOM involves co-registering of the interictal to the ictal SPECT image, originally by using a surface matching technique, but subsequently employing voxel matching methods (Brinkmann et al., 2000; O'Brien et al., 1998b, 1999a,b). The normalized interictal image is subtracted from the normalized ictal image to derive the difference (subtraction) in cerebral blood flow related to the partial seizure. Thresholding of the subtraction image to display only the pixels with intensities greater than 2 S.D. above 0 is performed. Finally, the images with intensities of more than two standard deviations are co-registered onto the structural MRI. Following implantation of subdural electrodes for chronic intracranial EEG monitoring the electrode positions can be segmented from a spiral CT scan and co-registered with the SISCOM image (So, 2000). This allows the determination of the relationship between the localized peri-ictal blood flow alteration and the ictal onset zone.

The SISCOM region of blood flow alteration is a surrogate for the localization of the epileptogenic zone independent of the pathological finding (O'Brien et al., 2000). The clinical parameters that are significant in determining the diagnostic yield of SISCOM include the duration of the seizure and the length of time of the injection from ictal onset (O'Brien et al., 1996, 1998a). The seizure should be at least 5–10 s in duration and the time from seizure onset should be less than 45 s (O'Brien et al., 1998a). The SISCOM findings also correlate with the operative outcome. Patients with a SISCOM alteration concordant with the epileptogenic zone are most likely to experience a significant reduction in seizure tendency if the focal cortical resection includes the region of peri-ictal blood flow change (O'Brien et al., 1998a, 2000). The disadvantages of a SISCOM study include the need for hospitalization and long-term EEG monitoring, the use of radioisotopes for two imaging procedures, and the required presence of habitual seizure activity. The indications for SISCOM in patients undergoing a presurgical evaluation include: non-substrate-directed partial epilepsy and conflicting findings in the non-invasive evaluation. SISCOM may be use to identify a "target" for placement on intracranial EEG electrodes (So, 2000). The presence of a SISCOM alteration may obviate the need for intracranial EEG recordings in selected patients. For example, patients with non-substrate-directed partial epilepsy of temporal lobe origin may not require chronic intracranial EEG monitoring if the extracranial ictal EEG pattern and peri-ictal SPECT studies are concordant. SISCOM also improves the diagnostic yield of post-ictal studies in patients with intractable partial epilepsy (O'Brien et al., 1999b).

The superiority of SISCOM in localizing the epileptogenic zone, particularly in extratemporal epilepsy, has been previously demonstrated (O'Brien et al., 2000). The prognostic importance of the SISCOM focus in patients undergoing a focal cortical resection for partial epilepsy of extratemporal origin has been evaluated (O'Brien et al., 2000). O'Brien and co-workers in a previous series evaluated the operative outcome in 36 patients with extratemporal epilepsy who had a SISCOM study prior to surgery (O'Brien et al., 2000). The presence of a localizing SISCOM alteration concordant with the epileptogenic zone was a favorable predictor of an excellent surgical outcome ($P < 0.05$) (O'Brien et al., 2000). Eleven of 19 patients (57.9%) with a concordant SISCOM focus and 3 of 17 patients (17.6%) with a non-localizing or discordant SISCOM, respectively, were rendered seizure-free or experienced only non-disabling seizures. Approximately, three-quarters of the patients with a localized SISCOM abnormality had a normal structural MRI. In addition, this study demonstrated that the extent of resection of the SISCOM focus was also of prognostic importance ($P < 0.05$) (O'Brien et al., 2000). Failure to resect the neocortical region intimately associated with the localized blood flow change concordant with the ictal onset zone was a predictor of an unfavorable operative outcome (O'Brien et al., 2000).

4. Epilepsy surgery

Surgical therapy has been shown to be safe and effective treatment for patients with medically refractory localization-related epilepsy (Awad et al., 1991; Cascino et al., 1993a; Cascino, 1996; Crandall, 1987; Dreifuss, 1987; Engel and Ojemann, 1993; Radhakrishnan et al., 1998; Van Buren et al., 1975). Patients with medial temporal lobe epilepsy and lesional epileptic syndromes may be the most favorable candidates for ablative surgical procedures (Awad et al., 1991; Cascino et al., 1993a; Cascino, 1996; Crandall, 1987; Dreifuss, 1987; Engel and Ojemann, 1993; Radhakrishnan et al., 1998; Van Buren et al., 1975). A minority of individuals with symptomatic partial epilepsy is rendered seizure-free with pharmacotherapy (Dreifuss, 1987; Cascino, 1996; Mattson, 1992). Approximately, 20% of patients with partial seizure disorders will experience socially, physically and medically disabling seizures (medically refractory seizures associated with an impairment in quality of life) (Cascino, 1996). The disabling effect of the seizures must be considered for each patient prior to considering surgical treatment. The frequency of seizure activity, type of seizure(s), co-morbidity, and underlying pathology are important variables that are used to determine the candidacy for surgical treatment. The psychosocial effects of the disease process should also be taken into account. The goals of epilepsy are to eradicate the seizure disorders, i.e. stop the seizures, avoid operative morbidity, and allow the individual to no longer be limited by the disease, i.e. work, attend school and/or live independently. Surgical treatment for intractable temporal lobe epilepsy has been demonstrated to be more effective than medical therapy (Wiebe et al., 2001).

The most common operative procedure involves resection of the epileptic brain tissue, i.e. focal corticectomy, in the anterior temporal lobectomy (Radhakrishnan et al., 1998). The rationale for surgical treatment is the excision of the epileptogenic zone, i.e. site of seizure onset and initial seizure propagation (Awad et al., 1991; Cascino et al., 1993a; Cascino, 1996; Crandall, 1987; Dreifuss, 1987; Engel and Ojemann, 1993; Radhakrishnan et al., 1998; Van Buren et al., 1975). These individuals may have a pathological substrate underlying the epileptogenic zone that may be identified using preoperative structural neuroimaging techniques (Table 1). The preoperative evaluation is constructed to identify the site of seizure onset and to determine the localization of functional cerebral cortex. Invariably patients undergo extracranial ictal EEG monitoring, neuropsychometry, visual perimetry, and cerebral arteriography (Table 2). The sensitivity and specificity of MRI in patients with localization-related epilepsy has been confirmed. The high diagnostic yield of MRI to "reveal" the common pathological alterations, e.g. post-trauma, vascular malformation, tumor, disorders of cortical development, mesial temporal sclerosis (MTS), has been demonstrated in patients undergoing epilepsy surgery (Table 1). The optimal tech-

Table 1
Surgically remediable epileptic syndromes

Selected epileptic syndromes	MRI	Siscom	Pathology
Substrate-directed			
Medial temporal lobe epilepsy	>90%	–	MTS
Lesional epilepsy: tumor	100%	–	Ganglioglioma, glioma, DNET
Lesional epilepsy: vascular	100%	–	Cavernous hemangioma, AVM
Lesional epilepsy: malformation	80–90%	–	FCD
Non-substrate-directed			
Neocortical (extrahippocampal)	0%	75%	Gliosis, focal cell loss, none

Adapted from Cascino (2001).

Table 2
Presurgical evaluation

Performed invariably	Performed variably	Performed selected centers
History and examination	Video-EEG (intracranial)	SISCOM
Routine EEG	Electrocorticography	MRS
MRI head	FDG-PET	PET receptor studies
Video-EEG (extracranial)	Interictal-Ictal SPECT	Functional MRI
Neuropsychology	Sodium amytal study	MRI volumetry

Performed invariably: almost always obtained prior to epilepsy surgery. Performed variably: available at most epilepsy centers, used in selected candidates. Performed selected centers: not widely available. MRI: magnetic resonance imaging; PET: positron emission tomography; SPECT: single photon emission computed tomography; SISCOM: subtraction ictal SPECT co-registered to MRI; MRS: magnetic resonance spectroscopy.

nique in adult patients with partial epilepsy must include coronal or oblique-coronal images using T1- and T2-weighted sequences (Cascino et al., 1992; Jackson, 1996). The most common imaging alteration in the adult with intractable partial epilepsy is medial temporal lobe atrophy with a signal intensity change. Fluid attenuated inversion recovery (FLAIR) sequences have been shown to increase the sensitivity of MRI to indicate a signal change (Cascino, 2001). Selected patients will require functional neuroimaging, i.e. PET or SPECT, and chronic intracranial EEG monitoring (Engel and Ojemann, 1993; Spencer, 1994; Theodore, 1996). A recent SPECT development, i.e. SISCOM, allows subtraction of the interictal-ictal scans and co-registration with a structural MRI (O'Brien et al., 1996) (Table 1). The outcome of epilepsy surgery is dependent on many variables including the age of seizure onset, location of the epileptic brain tissue, underlying pathology, and surgical strategy (Radhakrishnan et al., 1998). Favorable prognostic indicators include an early age of seizure onset, medial temporal lobe seizure onset, and pathologically-identified MTS or foreign-tissue lesion (Awad et al., 1991; Radhakrishnan et al., 1998). Greater than 80–90% of patients with medial temporal lobe epilepsy or lesional epilepsy may be rendered seizure-free or near seizure-free following a total excision of the epileptogenic zone. Less favorable operative candidates include patients with non-lesional extratemporal epilepsy. A SISCOM may improve the operative outcome in patients with non-lesional extratemporal seizures (O'Brien et al., 1998a).

The presurgical evaluation in patients with substrate-directed partial epilepsy is designed to determine the epileptogenicity of the neuroimaging alteration (Engel and Ojemann, 1993). The rationale for the electrophysiological studies is essentially confirmatory in patients with unilateral MRI-identified mesial temporal sclerosis or an isolated foreign-tissue lesion. Video-EEG monitoring is performed in these individuals to confirm the diagnosis of a partial seizure disorder, establish the seizure-type, and determine the disabling effect of the ictal behavior. Functional neuroimaging procedures may not be necessary in patients with medial temporal lobe epilepsy or lesional epilepsy in the presence of a structural MRI abnormality that is concordant with the remainder of the presurgical evaluation. Both MRS and PET have a high diagnostic yield in patients with temporal lobe epilepsy. These techniques may be most useful in patients with indeterminate structural MRI studies, e.g. no intra-axial abnormality of bilateral hippocampal atrophy. In patients with non-substrate-directed partial epilepsy there are significant concerns regarding the localization of the epileptogenic zone. Chronic intracranial EEG monitoring may prove necessary in these patients, especially with extratemporal epilepsy. Identification of a localized SISCOM focus may be a reliable indicator of the ictal onset zone (Tigaran et al., 2001). SISCOM may reveal a localized region of cerebral hyperperfusion or hypoperfusion in approximately 80% of patients with intractable partial epilepsy (Brinkmann et al., 2000; Fessler et al., 2000; O'Brien et al., 1998b, 1999a,b; So, 2000; So et al., 2000). The SISCOM findings are also predictive of operative outcome. Ultimately, a decision regarding surgical treatment must be based on a convergence of the neurodiagnostic evaluation (Tigaran et al., 2001). Electrophysiological studies must performed to localize the ictal onset zone in these patients. Resection of the SISCOM focus may be necessary to significantly reduce the seizure tendency in patients with a localized abnormality that is concordant with the epileptic brain tissue (Tigaran et al., 2001).

The financial expense associated with the preoperative evaluation and surgical treatment is considerable, range, US$ 30,000–100,000. This cost, however, must be compared with the expense of intractable epilepsy that includes antiepileptic drug therapy, office visits, laboratory studies, and unemployment. The putative beneficial effect of surgery is an improved quality of life that allows the individual to become a participating and productive member of society.

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