Fighting Fire with Fire: Surgical Options for Patients with Drug-Resistant Epilepsy

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ABSTRACT

While antiepileptic drugs (AEDs) provide adequate seizure control for most patients with epilepsy, ~30% continue to have seizures despite treatment with two or more AEDs.[1] In addition to direct harm from seizures, poor epilepsy control correlates with higher mortality, morbidity, [2, 3] and cost to the healthcare system.[4] In the subset of patients with persistent seizures despite medical management, surgical intervention and neuromodulation may be more effective. Primary care physicians and general neurologists should be aware of non-AED treatment options that are standard of care for drug-resistant epilepsy (DRE).

KEYWORDS: Drug-resistant epilepsy, surgical treatment of epilepsy, vagal nerve stimulation, responsive neuro-stimulation

DRUG-RESISTANT EPILEPSY: ITS CONSEQUENCES

Epilepsy affects ~1% of the United States population.[1] Despite an expanding selection of AEDs, many patients continue to have seizures, even with AED polypharmacy.[1] The International League Against Epilepsy (ILAE) defined drug-resistant epilepsy (DRE) as failure of adequate trials of two appropriate, well-tolerated antiepileptic medications (whether as monotherapies or in combination) to achieve sustained seizure freedom.[5]

DRE is associated with higher long-term morbidity and mortality[3] including sudden unexplained death in epilepsy (SUDEP), accidental injury and death, cognitive decline, as well as psychiatric and psychosocial comorbidities.[2] SUDEP is defined as non-traumatic, non-drowning-related sudden death in a person with epilepsy which may or may not be related to recent seizure but is not due to status epilepticus, with autopsy that is unrevealing of an obvious anatomic or toxic cause of death,[6] and is thought to be related to seizure-induced cardiac arrhythmias. SUDEP is the most common epilepsy-related cause of death, with an incidence of up to 9.3 deaths per 1000 person-years among some with DRE.[6] The strongest risk factor for SUDEP is recurrent seizures.[6]

Seizures impede patients' freedom to pursue education and careers,[7] drive,[6] and live independently. AED side effects can also adversely affect quality of life (QOL),[8] and have implications for patients' overall health. Patients with DRE require more ER visits and hospitalizations, longer hospital stays, more office visits, and accumulate up to double the healthcare costs of those with stable epilepsy.[4]

EPILEPSY CENTERS

Neurologists differentiate seizures that are "generalized" in onset (e.g. seizures arising from the entire brain at onset) from those that are "focal" or "partial" (e.g. seizures starting from one part of the brain). Classification systems for epilepsy are complex, relying on factors including clinical history, physical examination, EEG and MRI findings. Therefore, all patients with epilepsy should have a neurologist, preferably one with additional training in epilepsy. The National Association of Epilepsy Centers (NAEC) recognizes four levels of epilepsy care. Level 1 care consists of evaluation at an emergency department or primary care office, while level 2 care involves assessment by a general neurologist. Levels 3 and 4 are offered at specialized epilepsy centers, which provide a comprehensive approach to DRE.[9] The NAEC recommends referral to an epilepsy center if seizure freedom is not achieved within one year of treatment.[9] Earlier referral is recommended if the epilepsy diagnosis is in question, or in the following additional situations: to distinguish epileptic from psychogenic non-epileptic events; to optimize seizure control in non-refractory patients; to integrate neurologic and psychiatric care; and to optimize AED management for family planning. Other epilepsy center services include surgical evaluation, counseling on epilepsy-related dietary modifications, and care for developmental disabilities. The Brown-Rhode Island Hospital Comprehensive Epilepsy Program is a level 4 epilepsy center.

PREOPERATIVE EVALUATION

DRE rates are higher in focal epilepsy (35%) than in generalized epilepsy (25%).[6] Some focal epilepsies are associated with an underlying lesion, such as a stroke, tumor or vascular malformation, whereas others lack an overt structural abnormality apparent on MRI. Feasibility of surgical intervention should be explored as soon as focal DRE is diagnosed, since intervention can result in seizure reduction or seizure-freedom, with associated potential benefits including improved morbidity and mortality, better QOL, improved

psychiatric outcomes, and decreased AED requirement.[1,3]

Preoperative workup includes long-term video EEG monitoring and high-resolution brain MRI. Further investigations can include positron emission tomography, single photon emission computed tomography (SPECT), magnetic resonance spectroscopy, subtraction ictal SPECT co-registered to MRI, functional MRI, and magnetoencephalography.[10] In many cases, patients initially diagnosed with 'non-lesional' epilepsy are found to harbor a subtle lesion using these techniques.

Neuropsychological testing is used to assess for potential preoperative cognitive impairments and to predict postoperative neuropsychological outcomes.[10] For patients with temporal lobe epilepsy (TLE), Wada testing defines language localization and risk-stratifies the patient regarding possible postoperative memory impairment.[10] This test involves anesthetizing one hemisphere while a neuropsychologist performs rapid testing to characterize language and memory function in the contralateral hemisphere.

Our epilepsy center conducts multidisciplinary conferences to review potential surgical candidates. This forum draws upon the expertise of specialists from epilepsy, neurosurgery, neuroradiology and neuropsychology departments to formulate an individualized approach for each patient. Depending on the patient's needs, the team may include other specialists such as a psychiatrist, nutritionist, and social worker.

After the first phase of preoperative testing, some patients are found to be good surgical candidates and are referred to neurosurgery. Other patients may be deemed poor candidates for resective or ablative surgery for various reasons, such as the determination that the seizure focus stems from an important structure needed for language or mobility, or the finding of seizures from multiple foci. However, recent advances in the treatment of epilepsy offer hope for patients facing these difficult situations. Alternatives include an ever-growing list of AEDs, hormonal treatments, low glycemic index dietary approaches, and neuro-stimulation devices.

SURGICAL OPTIONS AND OUTCOMES IN EPILEPSY

Temporal lobe epilepsy (TLE) is among the most common focal epilepsies,[11] and is sometimes associated with scarring of the mesial structures including the hippocampus, called mesial temporal sclerosis (MTS). TLE is the focal epilepsy syndrome most amenable to surgery, and anterior temporal lobectomy (ATL) is the most common epilepsy surgery.[12] Therefore, many studies of surgical outcomes in focal epilepsy have emphasized the study of TLE patients who undergo ATL. Classically, ATL consists of the removal of some anterior-lateral temporal cortex plus resection of the amygdala, para-hippocampal cortex, and hippocampus.[9,12] Many such patients have MTS demonstrated on MRI and this subgroup has historically done extremely well with surgical intervention. More recently, selective ablation of the mesial temporal lobe structures (hippocampus and amygdala) using laser-thermal technology has demonstrated nearly equivalent outcomes for seizure control and improved neuropsychological outcomes due to sparing of lateral neocortical structures and adjacent white matter tracts.[13, 14] Other surgeries for focal epilepsy include topectomy, in which cortex is removed while sparing underlying white matter, as well as lesionectomy, extratemporal lobar or multilobar resections, multiple subpial transection, and hemispherectomy.

In a landmark randomized controlled trial (RCT) of surgical versus medical management in patients with drug-resistant TLE, resection resulted in seizure-freedom in 58% when evaluated one year after surgery, compared with 8% with medical management;[7] a second RCT demonstrated 73% seizure-freedom after two years of follow-up among patients who had surgery within two years of developing DRE, compared with 0% seizure-freedom in medically-managed patients.[1] Approximately 45% of patients were seizure-free after resection for extra-temporal lobe epilepsy.[1]

Data suggest that the earlier the surgery, the better the outcome.[1] Sex and age do not affect surgical outcomes.[1] While older age was previously thought to be a relative contraindication to epilepsy surgery, a retrospective analysis of ATL for MTS showed that age at surgery did not independently affect seizure recurrence.[8] Although patients with an identifiable lesion are more likely to experience postoperative seizure reduction or seizure freedom,[1] patients with non-lesional DRE can also benefit from surgery if seizures are well-localized on EEG.

Even when patients do not achieve total seizure-freedom postoperatively, reduction in seizures can be quite significant. A meta-analysis of studies of medically refractory TLE cases treated with surgical resection at 13 centers, 67.2% of patients achieved seizure-freedom and an additional 20% experienced improvement.[7] Thus, 87% of the patients achieved significant seizure reduction with surgery. Many patients with DRE experience numerous seizures each day, so reduction in seizure burden can be life-changing for patients and caretakers. Additionally, a systematic review of QOL for adults after epilepsy surgery has shown that QOL is significantly improved after surgery, with the most significant gains seen in those attaining seizure-freedom.[1]

NAEC-published data indicates that of the ~750,000 patients in the USA with DRE, a mere 2,459 patients, on average, underwent resection surgery each year from 2012 through 2015.[15] Several factors limit the identification and treatment of potential surgical candidates. First, many with DRE are not referred to an epilepsy center. DRE patients also vary in the degree to which seizures are disabling, and may forgo evaluation if the patient and treatment team feel that the seizures are not disruptive or limiting to quality of life.

SURGICAL RISKS AND ALTERNATIVES

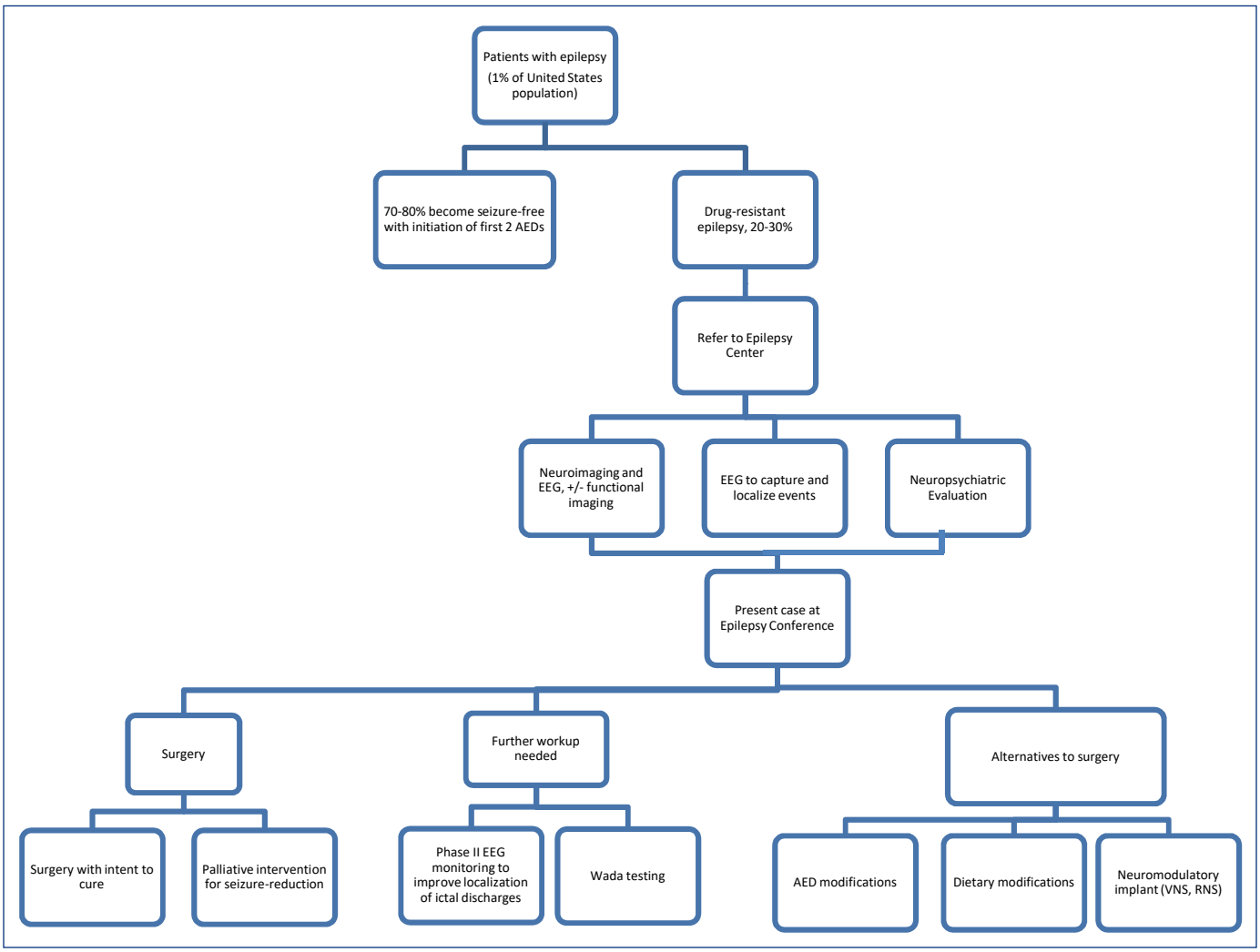
Risks associated with epilepsy surgery are defined by the location of the epileptic focus. For example, TLE surgery is

associated with risks of language deficit, memory impairment, motor impairment, visual field cut, cranial nerve injury, and behavioral/personality changes depending on the location of the focus.[10] With newer, less invasive and more tissue-sparing techniques for epilepsy surgery, the incidence of these has decreased. Reviews of epilepsy surgery have shown that operative mortality ranges from 0.1% to 0.5%.[1]

Apart from resective surgery, alternative options include vagus nerve stimulation (VNS) or responsive neuro-stimulation (RNS). VNS is an option to treat DRE which is not amenable to conventional resection, and for patients with persistent DRE after surgical resection.[12] VNS implantation involves surgical placement of a generator below the clavicle, with a stimulating wire connected to the left vagus nerve, to deliver intermittent stimulation.[12] The mechanism of action of VNS is speculated to relate to desynchronization of cortical activity.[16] A meta-review of 14 VNS outcomes studies demonstrated that ~50.9% of patients achieved a >50% reduction in seizure frequency.[16] The efficacy of VNS increases over approximately two years following implantation.[17] Bilateral or multifocal epilepsy may be associated with even better VNS outcomes.[18] Common but generally tolerated side effects include hoarseness and neck-tingling.[16]

RNS was FDA-approved in 2013 for patients 18 years or older with focal DRE and no more than two epileptic foci. RNS implantation involves neurosurgical placement of subdural or depth electrodes near the focus. Seizure pattern-detectors in the device are programmed to trigger direct cortical stimulation upon detection of an ictal buildup.[19] Electrical stimulation at the onset of ictal discharge is intended to interrupt propagation of the discharge before the seizure generalizes and the patient becomes symptomatic. The RNS System Pivotal trial, a multicenter RCT to evaluate short-term efficacy of RNS versus sham treatment, demonstrated a 37.9% decrease in mean seizure frequency in the treatment group, compared to 17.3% seizure reduction in the control group.[17] Patients receiving RNS treatment demonstrated statistically significant improvements in verbal functioning, visuospatial ability, memory, social function, health concerns, and

Figure 1. General approach to evaluation in DRE



cognition at one and two years post-implantation.[19] There were also significant improvements in QOL scores.[19] Some common complications and side effects of RNS noted during the Pivotal trial included implant site pain, local swelling or infection, headache, and dysesthesia.[19] Another disadvantage is the necessity of repeated surgery for battery changes, with an average battery life of 3.8 years.

CONCLUSIONS

The care of patients with DRE necessitates a multidisciplinary approach with integrated access to specialized diagnostic tools that guide the care team toward individualized treatment plans for each patient. Surgery is helpful for a subset of DRE patients. Many patients can achieve seizure-freedom after surgery. In those not achieving complete seizure-freedom, surgery can lead to a meaningful reduction in seizures, reduce risk of seizure-associated injury, and allow for reduction in medication burden. Even when the patient is disinterested in or hesitant to pursue surgery, referral to an epilepsy center can help to optimize the AED regimen, manage comorbidities and AED complications, manage key life transitions that affect epilepsy care, and explore neuromodulation among other options.

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