

BEYOND AEDS – SURGERY, DEVICES, DIET, OR MARIJUANA?

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How can I identify patients at risk of medical intractability?

Dlugos and colleagues studied 162 children with temporal lobe epilepsy for factors that are predictive of medical intractability at two years after epilepsy onset. They found the following independently predictive factors:

- 1) failure of first AED tried (odds ratio of 93.8)
- 2) presence of early risk factors for epilepsy; i.e. any of the following before 5 years of age: head trauma with loss of consciousness of >30 min, meningoencephalitis, neonatal seizures, or febrile seizures (odds ratio of 6.6)
- 3) temporal lobe MRI abnormality (odds ratio of 4.1)

Overall, the most important predictor of medical intractability in both adults and children is when seizures are difficult to control early in the course of the epilepsy. This feature may be evident as failure of the first AED to control seizures, or failure for seizures to be controlled in the first year of treatment.

How do I tell that my patient truly has medically intractable epilepsy?

The following is a checklist to help in deciding that your patient's epilepsy is indeed medically intractable:

- Diagnosis is correct
- AED used is appropriate to seizure-type
- Doses of at least two AEDs had been optimized
- Compliance has been good
- Not due to major co-morbidities, e.g. severe medical, sleep, or psychiatric disorders
- No seizure-aggravating drugs or circumstances

Who is the ideal surgical candidate?

Epilepsy surgery would be ideal if the chance of seizure control following surgery is very high, and the risk of complications is very low. Therefore, the following are features of patients who are ideal epilepsy surgery candidates:

- Well-circumscribed MRI lesion
- Well-localized inter-ictal discharge
- Clinical features of seizures indicate focal onset
- Concordance of above features
- Low risk of neurological deficit with surgical resection of focus
- Absence of other potentially epileptogenic foci

These patients can be said to belong to the “surgically privileged” group of candidates for epilepsy surgery. These patients should be considered for epilepsy surgery evaluation as soon as their seizures failed to be controlled with the second appropriate AED, and the seizures are interfering with their quality of life.

What if my patient is not the “ideal” epilepsy surgery candidate?

Patients who do not fall into the “surgically privileged” group can still be considered for epilepsy surgery because their intractable epilepsy may still respond to surgery. Examples of patients in this “*surgically responsive*” group are those with the following situations:

- Nonlesional epilepsy, especially if extratemporal
- Multiple lesions (e.g. multiple cavernous angiomas or tubers, or bilateral hippocampal atrophy)
- Epileptogenic focus at eloquent cortical regions
- Large multilobar lesions
- Epileptic spasms /atonic seizures

In the absence of an MRI-detected epileptogenic lesion, the probability of excellent postsurgical outcome (seizure-free, or auras only, or rare breakthrough seizures) with temporal lobectomy is about 60% to 65%, with or without concordant interictal epileptiform discharges. Compared with nonlesional temporal lobe surgery, nonlesional extratemporal surgery is associated with even lower chance of seizure freedom at approximately 25% to 50%. However, another 15% may have very good, though incomplete, seizure control. Functional imaging and electrophysiologic tests should be exploited to detect abnormalities that are associated with cortical epileptogenicity (e.g. PET, SPECT, MEG). The integration of these multiple localizing tests in seizure localization and surgical planning is essential in achieving favorable long-term outcome.

Unless clinical, EEG, MRI and functional imaging findings collectively provide concordant evidence of the seizure onset focus, intracranial EEG is generally required for these challenging epilepsy surgery cases.

Situations that require the consideration of intracranial EEG recording are as follows:

1. MRI does not show a potentially epileptogenic lesion, or it shows multiple potentially epileptogenic lesions.
2. Interictal extracranial EEG shows no epileptiform discharges, or it shows multifocal epileptiform discharges
3. Extracranial EEG recording shows indeterminate seizure onset or apparently multifocal onsets.
4. Standard noninvasive procedures disclosed results that are inconclusive or conflicting with each other.
5. Seizure focus identified by standard noninvasive procedures is diffuse, or proximate to cerebral areas with critical function (e.g., peri-rolandic and occipital regions).

MRI-Guided Laser Thermal Ablation (Visualase) . Instead of resecting epileptogenic lesions, thermal ablation has been performed with a probe that is guided into the lesion by intraoperative MRI imaging. The “minimally invasive” ablation can be tailored to the extent and shape of the lesion. Advantages of this ablation technique are lower postoperative morbidity and shorter hospital stay. The technique is considered especially suitable for lesions such as hypothalamic hamartomas, mesial temporal sclerosis, and cortical dysplasias, especially when they are not easily accessible for resection. Short-term postoperative seizure outcome in ablation of hypothalamic hamartomas is about 85%. Ablation of mesial temporal sclerosis is associated with short to mid-term seizure-free outcome of 50% to 60%, but long-term outcome result is awaited.

What surgeries could alleviate catastrophic epilepsy, even if the chance of complete seizure control is not high?

There are intractable epilepsies where seizures have catastrophic effects on the physical, mental or psychological well-being of the patient and the family, and yet, the patients are not good candidates for focal resective surgery or hemispherectomy. Surgical options for these patients include corpus callosotomy, multiple subpial transection, and device-based treatment.

Corpus Callosotomy

Seizure-types that could be alleviated by corpus callosotomy are the following:

- Generalized Tonic-Clonic Seizures
- Tonic Seizures
- Atonic Seizures
- Recurrent Generalized Status Epilepticus
- Absence Status Epilepticus

Multiple Subpial Transection (MST) – MST is used when a seizure focus cannot be completely resected because of presence of important cortical function at the region, such as language or motor function. Instead of resecting the focus, several transections of the short internuncial horizontal fibers are made, with the objective of desynchronizing the epileptogenic activity at the focus. With this approach, the vertical fibers are disrupted to a lesser extent, thus preserving to some extent the integrity of long tracts in the cortico-spinal system. A recent study compared Landau-Kleffner Syndrome and other electrical status epilepticus during sleep (ESES) patients who had MST, with those who did not. The investigators did not find any difference between the two groups in language, non-verbal ability, adaptive behavior, seizure frequency, ESES outcomes, or quality of life.

Devices

Vagus Nerve Stimulation (VNS) – VNS treatment is effective for a wide range of seizure-types. Median seizure frequency reduction of 50% is achieved in about 50% of the VNS patients, but only 4% to 5% became seizure-free. Seizure improvement of a remarkable degree usually does not occur until a few months of gradual increment of the stimulation pulse intensity or frequency. The interval between office visits for adjusting VNS settings should be optimized according to the patient's seizure frequency and adverse effects if present. *Infrequent adjustments, relative to the patient's seizure frequency, will lead to slow or no response, which may discourage patients from continuing VNS use.* Some adverse effects are dysphonia, pain or discomfort at the anterior neck. Bradycardia and vomiting or retching is very uncommon.

Sudden discontinuation of VNS use can be followed by seizure exacerbation when seizures had been improved by its use. Therefore, VNS settings and battery reserve should be monitored at least every 6 months, and more frequently depending on the age of the battery and the frequency and strength of the stimulation pulse used.

Responsive Neurostimulation (RNS) – With the phenomenon of “fighting fire with fire,” a technique was developed to detect EEG activity of the patient's habitual seizure, which will then trigger the delivery an electrical pulse to that focus to end the seizure (Neuropace company). Of the 256 implanted subjects, about 50% of the subjects followed to 3 years had 50% or greater reduction in seizure frequency during the last 6 months of follow-up. 3% had non-seizure related intracranial hemorrhages. Seizure freedom is rare.

What if my patient is not a candidate for any type of epilepsy surgery or devices?

Ketogenic diet emphasizes fat metabolism rather than carbohydrate metabolism, in order to increase ketones in the body. Thus, deviation from the diet plan by consuming more carbohydrates than allowed may result in loss of the seizure improvement. 40% of the patients benefited from the diet with at least 50% seizure frequency reduction, and 5% to 10% became seizure-free at one year follow-up. *Ketogenic diet is effective for a wide spectrum of focal and generalized epilepsies. There are a few syndromes that respond particularly well to ketogenic diet.* They are myoclonic-astatic epilepsy (Doose syndrome), Dravet's syndrome, tuberous sclerosis, Rett's syndrome, GLUT1 deficiency and pyruvate dehydrogenase deficiency. Both clinical and laboratory monitoring should be performed to reduce the risk of complications from the diet. Complications include weight loss or growth failure, acidosis, constipation, nausea, dehydration, nephrolithiasis, hypoglycemia, lipemia, pancreatitis, cardiomyopathy, and deficiency in vitamins, trace elements or minerals (hyponatremia, hypomagnesemia). Absolute contraindications to ketogenic diets are the different types of carnitine deficiencies, pyruvate carboxylase deficiency, porphyria, and the α -oxidation disorders.

Atkins diet, and modified versions thereof, is less restrictive in caloric intake than the classic ketogenic diet. However, about 30% of patients dropped the diet within three months of its initiation. Another diet therapy that liberalizes carbohydrate intake has been reported in relatively small studies to be just as effective as the classic ketogenic diet in improving seizure control. This diet, called the low glycemic index diet, permits the consumption of complex sugars that are less likely to raise blood sugar. This diet may be more palatable to adult patients, but more long-term data are needed from well-designed studies to demonstrate its benefits and limitations in treating intractable epilepsy.

The ingredient of interest in marijuana that has anticonvulsant properties is cannabidiol (CBD). Unlike tetrahydrocannabinol (THC), which is a major ingredient with psychoactive effects, CBD is not psychoactive. In lieu of waiting for the results of a scientifically rigorous study of CBD as an anti-seizure medication, many states have set up programs to allow use of artisanal marijuana or derived CBD for epilepsy with varying eligibilities and requirements. Based on currently available evidence and information, the following is what I have been counseling my patients.

- About 50% of patients have $\geq 50\%$ reduction in seizures during short-term follow-up, typical of non-blinded or anecdotal series of AEDs
- Seizure-freedom is uncommon: $\approx 10\%$
- More responsive in Dravet & LGS
- Adverse effects: $\approx 20\%$ diarrhea, somnolence; drug interactions is an issue not fully recognized.
- Rigorous scientific data are still lacking
- FDA: Artisanal MJ has varying CBD amount
- Long-term adverse effects, drug interactions and pregnancy not known
- Out of pocket cost could be \approx \$500 to \$1500 per month

I also tell my patients that the following are situations not appropriate for marijuana or CBD use.

- First seizure or new-onset epilepsy
- When less than two antiepileptic medications have failed
- Patients who are seizure-free on existing medications
- When the diagnosis of epilepsy is unclear
- As a single agent
- In patients with poor compliance with established therapies
- As an alternative to epilepsy surgery or evaluation

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