Epilepsy Update - Medically Refractory Epilepsy

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Questions
International League Against Epilepsy

- At least 2 unprovoked seizures more than 24 hours apart
- One unprovoked seizure and a probability of further seizures similar to the recurrence risk after two unprovoked seizures over the next ten years
- Diagnosed with an epilepsy syndrome

Focal instead of partial
Focal evolving to bilateral convulsive seizure
Partial, complex partial and secondary generalized seizures are terms that are no longer recommended
2.2 million people in the United States have active epilepsy
Approximately 60% of these are focal onset
1:26 people in the U.S. will be diagnosed with epilepsy in their lifetime
150,000 new cases diagnosed in the U.S. per year

Hauser WA, et al. Epilepsia 1993; 34: 453-468
Incidence of newly diagnosed epilepsy is highest in patients < 15 years of age and > 60 years of age.

In the > 60 years old cohort:
- Vascular etiology 49%
- Idiopathic 32%
- Degenerative 12%
- Brain tumor, Trauma, Congenital, Infectious

Hauser WA, et al. Epilepsia 1993; 34: 453-468
Epilepsy Treatment

- Antiepileptic drugs
- Resective or Palliative Brain surgery
- Neuromodulation (VNS, RNS)
- Dietary Therapies (Ketogenic diet)
Treating Patients with Epilepsy

- History and Physical Exam (particularly history from observers, often videos are helpful)
- AED trials (why did they fail- cost, noncompliance, side effects, poor efficacy)
- Imaging- particularly 3T MRI with seizure protocol
- EEG- including routine, ambulatory and LTVM
Epilepsy Treatment

Considerations

- Type of epilepsy
- Comorbidities
- Mechanism of action of AEDs
- Drug interactions
- Side effects of medication/therapy
Approximately 50% of patients will obtain seizure control with a single antiepileptic drug monotherapy.

13% will get control with a second AED monotherapy trial.

24% will get control with an adjunctive therapy.

Available drugs

- Benzodiazepines, Dilantin, Depakote, Phenobarbital, keppra, lamictal, topamax, onfi, briviact, vimpat, potiga, banzel, ethosuximide, aptiom, carbemazepine, trileptal, fycompa, sabril, felbatol.
Drug Resistant Epilepsy

- Patient’s with continued seizures after trial of 2 or more AED (estimated approximately 15-30%)
- Importance of Identifying Patient’s with Drug Resistant Epilepsy
  - Seizure related injuries
  - Increased healthcare utilization
  - Adverse effects of AEDs
  - Impaired cognition
  - Caregiver burden
  - Impaired quality of life due to inability to drive etc.

Drug Resistant Epilepsy- Causes?

- Hypotheses
  - Transporter hypothesis- overexpression of drug efflux transporters at epileptogenic focus
  - Target hypothesis- alteration of cellular targets of antiepileptic drugs results in decreased sensitivity to the medications

US Estimates
- 870,000 patients with DRE (failed 2 or more AED)
  - 60,000 referred to EMU (epilepsy monitoring unit)
    - 3000 to surgery, 4000 VNS, 3000 with diet changes
    - 50,000 either not DRE or continued on medical treatment

This leaves an estimated 810,000 patients in the U.S. per year who are continued on AED without further evaluation

CDC data from 2015
Drug Resistant Epilepsy- Goals

- Confirm the diagnosis of refractory epilepsy with LTVM (differential diagnosis includes non epileptic seizures, syncope, cardiac etiology among others)
  - 20-30% of patients referred for LTVM do not have refractory epilepsy
- Improve long term seizure control
- Improve quality of life
- Reduce side effects of treatment

Chances of a 3\textsuperscript{rd}, 4\textsuperscript{th}, 5\textsuperscript{th} medication trial controlling seizures adequately continue to drop and overall only 15-20\% of patient’s with DRE will respond to additional medication trials.

Predictors of refractory seizures:
- History of status epilepticus
- Frequent GTC seizures
- History of neurological insult
- Duration of epilepsy
- Developmental disability

Drug Resistant Epilepsy-Treatment plan and goals

- AAN Quality of Care Measures recommend:
  - Assessment for surgery referral should be considered every 3 years for patients with intractable epilepsy
  - Referral to EMU for LTVM should be considered in these patients earlier rather than later since this is the first step in evaluation for other treatment options for epilepsy
  - Currently the average length of time it takes for clinicians to refer to EMU is estimated at 20 years
Treatment Options for DRE

- Further medication trials
- Surgery - resective or palliative
- Neuromodulation - VNS, RNS
- Diet - Ketogenic, modified Atkins, low glycemic
Palliative surgery—typically with continued refractory epilepsy (included corpus callosotomy and hemispherectomy)

Resective surgery

- Should be the first line therapeutic consideration for DRE
  - Clearly amenable
    - Mesial temporal sclerosis
    - Focal cortical dysplasia
    - Other lesional epilepsy

Presurgical evaluation

- Seizure protocol MRI
- Video EEG monitoring
- PET
- Neuropsych
- fMRI/WADA (particularly if concerned for eloquent cortex)
- Possibly ictal SPECT and MEG
- Invasive EEG recording (subdural electrodes or depth electrodes)
Surgical Evaluation

- LTVM and invasive monitoring should be done even if no lesion found on MRI
- Favorable outcomes are still possible if an area of cortex can be localized particularly for frontal lobe epilepsy

Cerebral Surgical Options

- Anterior Temporal lobectomy
- Lesionectomy
- Multiple subpial resections, Stereotactic Laser Ablation, Responsive Neurostimulation (in areas when epileptigenic focus is near eloquent cortex)
- Palliative surgical options (CC, hemispherectomy)
Predictors of surgical success

- Epileptogenic focus clearly localized on EEG
- Seizures are disabling
- Epileptogenic focus away from eloquent cortex
- Low risk of memory loss and other cognitive changes based on neuropsych evaluation +/- WADA
- Patients with lesions on MRI are 2.5 times more likely for seizure freedom following surgery than those without MRI lesion

Non-dominant temporal lobe
   • 6-6.5 cm from the temporal pole with amygdala and hippocampus

Dominant temporal lobe
   • 4-4.5 cm from the temporal pole

At one year 53% of patient’s treated surgically had seizure freedom compared to 8% of patients with continued best medical therapy
Patients who received surgery within 2 years of being diagnosed with DRE did better

73% of patients treated surgically within 2 years had seizure freedom at two years follow up

0% of patient in the continued medical therapy group had seizure freedom at 2 years of follow up

Delivers constant stimulation to the left vagus nerve

Proposed mechanism of action is that these stimuli desynchronize thalamocortical activity reducing seizures

Approved in 1997 for treatment of refractory focal onset seizures in patients age 12 or older

VNS data

- Approximately 50% of patients get at least a 50% reduction in seizure frequency
- Decreases seizure frequency, duration of seizures, more alertness, less cognitive impairment, and duration of the post ictal period
- Provides increased seizure reduction over years (increased seizure reduction over 12 months and up to 10 years)
  - PuLsE trial (Open Prospective Randomized Long-term Effectiveness Trial)
  - VNS with best medical practice improves QOL measures

Vagus Nerve Stimulator

Clinical and Economic impact of VNS

- Decreases use of healthcare resources (ER visits, hospital days and head trauma among other visits)
- Decreases Epilepsy comorbidities
- Decreases healthcare costs after year 1.5 (savings of at least 50,000 at year 3 on average)

Responsive Neurostimulation (RNS)

- Approved in 11/2013 for treatment of refractory epilepsy in patients older than 18yo and with 2 or less epileptogenic foci
- Electrodes are implanted near the epileptogenic focus with subdural strips or depth electrodes
  - Programmed to detect seizures and deliver a direct stimulus to cortex when seizures are detected
    - 37.9% reduction in mean seizure frequency versus 17.3% in sham group
    - 44% reduction at 1 year and 53% at 2 years long term follow up
- Stimulation of the anterior nucleus of the thalamus under study and not yet approved

Dietary Therapy

- **Ketogenic diet**
  - Low fat, low carbohydrate diet that induces ketosis while preserving caloric intake
    - 3:1 or 4:1 fat to carbohydrate/protein ratio
    - Use medium to long chain fatty acids with calorie and fluid restriction
    - 38% of patients with more than 50% reduction in seizures at 3 months and 50% at one year
  - Problems- high drop out rate for the diet particularly ineffective with adults

- **Modified Atkins diet and Low glycemic index**

Final Thoughts

- Drug-resistant epilepsy is poorly identified by clinicians
- Referring patients to EMU early to help identify truly DRE patients is important to better clarify treatment options and stop prolonged unnecessary treatment
- Early identification of resective surgical candidates often leads to better outcomes
- Considering non resective and non medication options often can lead to better seizure control and better QOL outcomes for patients