INTRACTABLE EPILEPSY: NEW OPTIONS IN 2012

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EPILEPSY

- MOST COMMON SERIOUS DISEASE CARED FOR BY NEUROLOGISTS
- 3% OF THE US POPULATION IS AFFECTED BY EPILEPSY
- IT HAS LONG BEEN A TREATABLE DISORDER
- BUT IT IS ALSO A CHRONIC DISORDER AND NOT EVERYONE WITH EPILEPSY RESPONDS TO TREATMENT
NATURAL HISTORY OF EPILEPSY

- ~70% of patients will have seizures completely controlled at some point
- ~20% will continue to have some seizures but be functional
- ~10% will be severely disabled by their epilepsy
INTRACTABLE EPILEPSY: NEW OPTIONS IN 2012

- Characterize INTRACTABLE or REFRACTORY EPILEPSY
- Consequences and significance
- Treatment options today
- Treatment options on the horizon
Refractory/Intractable Epilepsy Def.

- **Seizures persist despite treatment** with at least 2 or 3 antiepileptic drugs tolerated at reasonable dosage
- **Minimum frequency of seizures**, such as e.g. 1 per month or every few months, without remissions for 6-12 months - or longer
- **Durations of 1-10 years** or more of such uncontrolled seizures
- **Substantially disabling** the individual
PREDICTORS OF EPILEPSY INTRACTABILITY

- Greater **number** of seizures prior to initiation of antiepileptic drug therapy (e.g. 3 versus 100)
- Higher seizure **frequency** (e.g. weekly versus yearly)
- Longer **duration** of epilepsy
- **Focal** versus **Generalized** Epilepsy
- **Structural/Metabolic** or **Unknown** versus **Genetic** etiology
Epilepsy-Related: Quality of Life

Sillanpää, 1990.
Consequences to Society: Costs

- High proportion of costs attributed to patients with intractable epilepsy - due mainly to lost productivity

In 1995 $12.5 billion in US

2010 - EPILEPSY TREATMENT OPTIONS

- ANTIEPILEPTIC MEDICATIONS
- EPILEPSY SURGERY
- NEURO-STIMULATION
- RADIATION THERAPY
- IMMUNOTHERAPY
- GENETIC THERAPIES
- PSYCHOLOGICAL/SOCIAL INTERVENTIONS
ANTIEPILEPTIC MEDICATIONS
Goal: No Seizures And No Side Effects

1. Determine the seizure or epilepsy type
2. Select the optimal class of drugs for that seizure type (efficacy is similar)
3. Choose medication with best side effect profile for that individual
4. Increase drug slowly to reasonable or maximal dosage
5. If unsuccessful change agents (once, twice or more)
6. If seizures persist, combine drugs (2 or 3 at most)
Response to Antiepileptics in Newly Diagnosed Epilepsy

- **First** antiepileptic: ~ 47% seizure-free
- **Second** antiepileptic ~ 13% seizure-free
- **Third or more** drugs or multiple drugs ~ 4%
  
  eventually become seizure-free

Therefore, if a patient fails to respond to 2 or 3 standard antiepileptic drugs, there is a very **low** probability of medication completely controlling the seizures.  
(Kwan, Brodie NEJM 2000;342:314)
## Classification of Seizures (ILAE 2010)

### A. Generalized Seizures
- Absence
- Myoclonic
- Clonic
- Tonic
- Tonic-clonic
- Atonic

### B. Focal Seizures
- Without impairment of consciousness (motor, sensory, autonomic)
- With impairment of consciousness (evolving to bilateral convulsive)

### C. Epileptic Spasms

### D. Unknown

### E. Unclassified
Primary Generalized Epilepsy
Primary Generalized Epilepsy EEG
Focal Epilepsy
Seizure onset - phase reversal theta at T2 (anterior temporal)
Antiepileptic Medications

- Phenytin - Dilantin.
- Phenobarbital.
- Carbamazepine - Tegretol.
- Valproate - Depakote.
- Ethosuximide - Zarontin
- Primidone - Mysoline.
- Benzodiazepines - Klonopin
- Acetazolamide - Diamox
- Lacosamide - Vimpat*
- Clobazam - Frisium**
- Felbamate - Felbatol.
- Gabapentin - Neurontin.
- Lamotrigine - Lamictal.
- Topiramate - Topamax
- Tiagabine - Gabatril.
- Levetiracetam - Keppra
- Zonisamide - Zonegran
- Oxcarbazepine - Trileptal.
- Pregabalin - Lyrica
- Rufinamide - Banzel*
- Vigabatrin - Sabril*
- Ezogabine - Potiga**
16b. Symptomatic Localization-related, Medically Stable Elderly Man or Woman
TAILOR THE DRUG TO BEST FIT THE INDIVIDUAL

- i.e. - MOST DRESSES OR SUITS WILL DO THE JOB, SO AN INDIVIDUAL’S PERSONAL PROFILE GUIDES THE CHOICE

- MOST AEDs HAVE SIMILAR EFFICACY FOR SEIZURE CONTROL, SO SIDE EFFECT PROFILES FOR THAT INDIVIDUAL LARGELY GUIDE THE CHOICE
AEDs – Cognitive Profiles

- **Best**
  - Lamotrigine
  - Levetiracetam
  - Valproate
  - Felbamate
  - Gabapentin
  - Lacosamide

- **Relatively Good**
  - Carbamazepine
  - Phenytoin
  - Oxcarbazepine

- **Intermediate**
  - Tiagabine
  - Zonisamide

- **Least Favorable**
  - Phenobarbital
  - Primidone
  - Topiramate
Special Considerations in Treating Women With Antiepileptic Drugs

- Fertility and ovulatory function, menstrual cycle regularity
- Hormonal contraception
- Pregnancy
- Teratogenic effects
- Breastfeeding
- Bone health


EPILEPSY SURGERY
Candidates for Epilepsy Surgery

- Intractable epilepsy
- Present for a substantial duration (usually years)
- Refractory to medical therapy
- Substantially impairing quality of life
- Benefit of surgery should outweigh the risks
Evaluation of Candidates for Epilepsy Surgery

- Localization of seizures by interictal \textit{EEG}
- Localization by brain imaging- \textit{MRI}, PET scanning
- Localization by \textit{video-EEG} monitoring of seizures (may combine with ictal SPECT)
- Localization by \textit{neuropsychological testing}
- \textit{Convergence} of localization data
MRI – Subtle Temporal Atrophy
Mesial Temporal Sclerosis
HETEROTOPIAS
Further Methods of Determining a Potentially Seizure Focus

- PET
- Depth electrodes
- Cortical grids or strips
- Ictal SPECT scans
- Nuclear magnetic resonance scans
- Magnetoencephalography
Extratemporal Subdural Grid
Types of Resective Epilepsy Surgery

- Temporal lobectomy
- Extratemporal resections (lobar: frontal, occipital)
- Corpus Callosotomy
- Hemispherectomy
- Multiple subpial transections
Temporal Lobectomy (AMTL)

Right anterior temporal resection
Controlled Trial of Surgery for Temporal Lobe Epilepsy

- Randomized 80 patients (40 medically and 40 surgically treated) with F/U at 12 mos.
- Significantly better outcomes for surgical group: 1) seizure-free, 2) decreased seizures, 3) improved quality of life (P<0.001)

NEJM 2001;345:311-8
History of Brain Stimulation for Epilepsy

- 1970’s - Cerebellar stimulation
- 1990’s to today - Vagus Nerve Stimulation (VNS)
- 1980’s and perhaps (?) again – Deep Brain (Thalamic) Stimulation (DBS)
- Reactive Neural Stimulation (RNS)
Vagus Nerve Stimulation (VNS)

- Approved by FDA in July 1997
- Patients with intractable epilepsy ≥ 12 yo
- First device approved to treat epilepsy

Courtesy of Cyberonics, Inc.
Benefits of Vagus Nerve Stimulation

- Seizures decrease 50% or more in 50% of patients
- Effect increases over time
- Seizure severity decreased
- Improved level of alertness (medication may be decreased)
- Few adverse effects - Hoarseness, infection (rare)
- Batteries require replacement every ~ 10 yrs
Neurostimulation
Proposed Mechanisms of Action for Vagus Nerve Stimulation

- Desynchronization of EEG
- Suppression of spikes
- Block ictal rhythmic build-up in a seizure
- Release of GABA and Glycine
- Effects on limbic and brainstem systems
Investigational Neurostimulation

- Deep Brain Stimulation (DBS)
- Responsive Neurostimulation (RNS) (Neuropace)
Deep Brain Stimulation

- Implanted with leads in the left and right anterior nucleus of the thalamus
- Wires leading to a dual-channel stimulator
Deep Brain Stimulation*

- More than 6 partial or secondarily generalized seizures per month
- Seizures refractory to more than 3 AEDs
- 4 phases: 3 month baseline, 3 mo double-blind phase, 9 mos open-label phase, long term follow up
- Responder rate significantly higher than controls and increases past 3 month trial (seizure reduction 29% greater in subjects versus controls)
- FDA considering approval

* Protocol
Responsive Neurostimulation

Responsive Neurostimulation

- Electrodes record intracranial EEG and input to an algorithm that determines if a seizure has started or may begin.

- Triggers focal electrical stimulation to prevent or stop seizures.
Responsive Neurostimulation

Seizure Detection - Examples

Stimulation Effect

Responsive Neurostimulation

- Randomized, double-blinded multicenter trial
- Enrollment of ~240 adult subjects
- Medically refractory partial epilepsy
- Average of 3 or more disabling seizures every 28 days
- Data showed some benefit but FDA is still considering approval
RADIOTHERAPY FOR EPILESPY

Gamma Knife

Target is the Temporal Lobe
POST RADIATION CHANGES
INFLAMMATORY & IMMUNE MECHANISMS IN EPILEPSY

**Infectious**
- Neurocysticercosis
- Viral encephalitis (herpes, EB, rotovirus, etc.)
- Mycoplasma pneumoniae
- Syphilis
- Chronic meningitis

**Autoimmune**
- Systemic lupus erythematosus
- Neurosarcoidosis
- Multiple sclerosis
- Rasmussen’s encephalitis
- Limbic encephalitis – paraneoplastic (*with or without antineuronal antibodies*)
  - post-viral
  - post vaccination
  - drug hypersensitivity
Figure 1 - Flair MR imaging showing hyperintense lesions in both medial temporal lobes and cingulate gyrus compatible with limbic encephalitis.
AUTOIMMUNE REFRACTORY EPILEPSIES

- Limbic encephalitis
- Anti-NMDA receptor encephalitis
- Antiglutamate receptor encephalitis
- Voltage Gated Potassium Channel (VGPK) Antibodies
- Anti-glycolipid antibody syndrome
- Hashimoto’s encephalopathy (autoimmune thyroid encephalopathy)
IMMUNOSUPPRESSIVE THERAPIES FOR REFRACTORY EPILEPSIES

- Corticosteroids
- Intravenous immunoglobulin
- Plasma exchange
- Cyclophosphamide
- Calcineurin antagonists
INTRACTABLE EPILEPSY: GENETIC IMPLICATIONS

- RISK FOR ADVERSE DRUG REACTION
- POTENTIAL FOR RESISTANCE TO DRUG THERAPY
- ANTIEPILEPTIC DRUG TARGETS
- SPECIFIC GENE THERAPY
GENETIC IMPLICATIONS & THERAPIES

Drug effects
- Carbamazepine serious adverse reactions associated with HLA-B*1502 allele in Asians
- Multiple drug resistance gene (MDR-1) MDR-1 has been demonstrated to be overexpressed in seizure foci of some drug-resistant patients.

Epilepsy control
- Some genetic epilepsies respond best to specific AEDs (e.g. ADNLE to CBZ ; JME to VPA)
- 21 genes associated with idiopathic generalized epilepsy – channelopathies- Na, Ca, K, Cl channels; GABA and Ach receptors
- Neuronal migration disorders – (e.g. Lissencephaly (LIS1, DCX)
POTENTIAL GENETIC THERAPIES

- GENE TRANSFER THROUGH VIRAL VECTORS
- GENE TRANSFER WITH BRAIN GRAFTS OF CELLS (e.g. – with specific inhibitory or excitatory transmitter effects)
Care for Epilepsy

- Diagnose properly
- Medical therapy
- Education and support
- Psychosocial RX
- Epilepsy surgery, etc...
- Maximize patient’s adjustment and coping strategies
CONCLUSIONS

- EPILEPSY IS A **TREATABLE** DISORDER
- THE GOAL OF TREATMENT SHOULD BE “NO SEIZURES AND NO SIDE-EFFECTS”.
- OLDER TREATMENTS WORK WELL FOR MOST PATIENTS (~70%)
- BUT WHEN SEIZURES PERSIST AND ARE INTRACTABLE …
- THERE ARE STILL MANY **RX OPTIONS**
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