Drug Resistant Epilepsy
Etiology and Management

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INTRUDUCTION

• Objectives:
  ➢ Approach
  ➢ Treatment options
Definition

• Some what elusive
• Interchangeable terms
• ILAE consensus
Incidence

- 20-30 % of ped.sz are RE.
- Seizure in gen.pop.0.6%
- Not changed even with the use of new AED.
- DRE: primary refractory 50%
- secondary refractory 35%
- relapsing remitting 15%

• The Epilepsia 2008;49:1230-8
Number of New Cases of Epilepsy per 100,000 Population

- Carlisle, England
- Copparo, Italy
- Northern Norway
- Faroe Islands
- Rochester, Minnesota, USA

No. New Cases

Age (years)

Hauser and Hesdorffer, 1990.
Causes of New Cases of Epilepsy

- 77% Idiopathic/Cryptogenic
- 3% CNS infection
- 4% CNS neoplasm
- 4% Head trauma
- 4% CNS defect at birth
- 1% Birth anoxia
- 5% Cerebrovascular
- 2% Other known causes

Hauser and Hesdorffer, 1990.
What are the predictors of DRE

Why?
Predictors

- AGE ONSET
- SEIZURE SEMIOLOGY
- DEVELOPMENT AND FHx
- P/E
- EEG
- NEUROIMAGING
- ETIOLOGY
AGE ONSET

- Acute symptomatic or neonatal status epilepticus.
- Onset at age 5-9yrs ass/w lowest risk.
- Onset <1 y age
- Onset after 15yrs
SEIZURE SEMIOLOGY

- sz frequency, duration
- Higher frequency of 2nd gen. sz.
- Long duration of epilepsy prior to treatment
- Combination of sz atonic, tonic, myoclonic
DEVELOPMENT AND FHx

- Abnormal development
- Regression
- Family history of DRE
- Neurologic abnormality on examination
- Microcephaly
- Focal deficit
- Alteration of tone
- Neurocutaneous stigmata
EEG

• Focal EEG slowing
• Variety of EEG abnormality
• Slow, burst suppression BG
• MFS, SSW, SBS, PS
NEUROIMAGING

• Focal lesion (MTS, Tu)
• Cortical dysplasia
• Malformation
• Vascular lesion
• Post traumatic
ETIOLOGY

• Identify cause predict prognosis and prevent intractability
• Symptomatic generalized syndromes carry the highest risk (50%)
• Specific epileptic syndrome (infantile spasm, LGS, SMEI PME, etc.)
• Treatable metabolic disorder
Mechanism of drug failure

1. Failure of drugs to reach their targets:
   (transporter hypothesis)
2. Alteration of drug targets:
   (target hypothesis)
3. Drugs missing the real targets
Mechanism of DRE

- Not known whether different bases or end of the spectrum of same mechanism.
- Several hypotheses:
  - Glia or neurons disturbances.
  - Kindling: reorganization 2ry to sz induced hypoxia.
  - Drug metabolism due to different Genetic properties. (ABCB1 p-glycoprotien polymorphism)
<table>
<thead>
<tr>
<th>Reason</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Wrong diagnosis</td>
<td>Syncope, cardiac arrhythmia, or other conditions; psychogenic nonepileptic seizures</td>
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<tr>
<td>Wrong drug (or drugs)</td>
<td>Inappropriate for seizure type; pharmacokinetic or pharmacodynamic interactions</td>
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<td>Wrong dose</td>
<td>Too low (overreliance on “therapeutic” blood levels); side effects preventing drug increase</td>
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<tr>
<td>Lifestyle issues</td>
<td>Poor compliance with medication; alcohol or drug abuse</td>
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Table 1. Some Reasons for Pseudoresistance to Antiepileptic Drug Therapy.
Patient referred as DRE

- Epileptic vs. Non-epileptic
- Non-epileptic event like syncope, and psychological, parasomnia & cataplexy.
- Both may coexist, up to 40%.
Non epileptic seizure
psudoseizure of emotional origin

• Resemble grand mal attack or have prominent motor component
• Bizarre posturing
• Extreme opisthotonos
• Eyelids forcibly closed
• Usually prolonged
• May be provoked by suggestion
• Model of epilepsy
• Difficult to control sz ,rapid onset without known cause
Nonepileptic event

- Coexist with epileptic sz in up to 40%
- 15% of admission into epilepsy monitoring unit are non-epileptic event, most of whom for diagnostic reasons.
- 80% of children vs. 40% of adult respond to psychological treatment.
Misdiagnosis

- Over and under diagnosis of epilepsy
- Smith et. al. 1999; 184 pt. With epilepsy, 94 investigated for RE
- 12 found to have psudoseizure. (12.7%)
- 16 pt. were under treated and controlled with dose adjustment. (17%)
- Overall misdiagnosis rate is 26%
Failure of treatment

- **Poor compliance**: many pills, complex dose schedule, lack of understanding.
- Wrong diagnosis
- Wrong treatment, or inadequate doses (30% of pt.).
- Factor may alter sz threshold are: pregnancy, menstruation period, stress, drugs…etc.
Principles of management

• Benefits of sequential AED utilization:
• Brodie MJ et al 2012

1098 adolescent and adult patients with a diagnosis of epilepsy were started de novo on AED treatment and followed up to 25 years (median of 7.5 years). With the first drug trial, 49 percent became seizure-free. A second medication trial produced remission in an additional 13 percent, while only a further 4 percent became seizure-free on a third medication regimen.

Even with new AED

AED

**Conventional agent**
1 Phenytin
2 Carbamazepine
3 Phenobarbital
4 premidone
5 Na-Valproate
6 benzodiazepine
7 ethosuximide
8 acetazolamide

**New agents**
1 vigabatrin
2 levetiracetam
3 topiramate
4 gabapentin
5 lamotrigine
6 oxcarbazepine
7 felbamate
8 pregabiline

**Newer agents**
1 lacosamide
2 eslicarbazepine
3 rufinamide
4 stiripentol
5 retigabine
6 brivaracetam
7 perampanel
Treatment

- Proper diagnosis lead to proper treatment.
  - CMZ/DHP worsen absence sz.
  - CMZ,DHP,VGB  may worsen gen. epi.
  - Gabapentin may precipitate myoclonic jerk
  - Benzodiazepines IV may cause tonic sz.
TREATMENT

Rationale for poly therapy:

- Use drugs with different mechanism of action.
- Synergetic effect
- Pharmacokinetic interaction
- Different side effect profile

12% of patient will achieve sz control with poly therapy, after trying several agent as a monotherapy.
Evaluation for Non Drug therapy

- EMU: scalp EEG
- MRI
- PET scan
- Ictal SPECT
- MEG
- Neuropsychology
- Psychology
- TEAM DISCUSSION
Subdural Grids/strips
Surgery

- Surgical options:
  - focal resection: surgically remedial syndrome MTS or hippocampal sclerosis (class I evidence)
  - Lesionectomy: glial tumor or cavernoma (class III evidence)
  - Non lesional resection (class evidence III)
Surgery

- Focal cortical dysplasia /
- Functional Hemispherectomy
- Palliative procedure
  Callosotomy
Treatment in eloquent areas: Multiple Subpial Transections
VNS

  - 3 prospective, blinded, controlled study have shown 20-30% reduction in sz frequency in 30% of patient, up to 50% with 18-24 m use.
  - Cycle frequency
  - Class I Evidence
  - Effective in children and adult
  - Indicated for drop attacks, patient who are not candidate for Sx (symptomatic generalized epilepsy, LGS).
  - Act by desynchronization of interconnected cortical neurons
  - It is a palliative procedure
Stimulation Technique

- Widely used intracranially in movement disorder patients, in epilepsy getting more often
- Thalamic stimulation has no role. Anterior nucleus of the thalamus: class I evidence
- 29% greater sz reduction than control
- At 2yrs 56% of pt, sz reduction >50%. and 14% sz free for 6 months or more. FDA for neurological device approved 2012
Ketogenic Diet

- Alternative therapy for epilepsy since 1920
- Less use after 1940, more use after 1994
- Mechanism of action not known
- Ketocal
- Ketosis
- Ratio 1:3 to 1:4
Complication

1-Constipation and GI upset
2-Renal stone 5%
3-Hyperuremia
4-Acidosis
5-Iaired phagocytosis with recurrent infection
6-Hypocalcimia and osteomalacia
7-Hyperlipidemia
8-Cardiac complication prolonged QT and arrhythmia
9-Drug complication: VPA
10-Hypoglycemia and vomiting

clinical efficacy

- 1998 Hopkins reported a prospective study, 150 pt, F/U 1 y, failed AED(6), age 1-16 y.
- 3m  6m  1y
  - % pt. On diet  83%  71%  55%
  - >90% improve  34%  32%  27%
  - >50% improve  26%  19%  23%
  - <50% improve  24%  19%  5%
- short term blinded crossover study in progress
Conclusion

• Correct diagnosis is the most important step. thus pseudoseizure is detected.
• Monotherapy is the key in the management
• EEG is important diagnostic and prognostic tool, should be used more frequently
• Surgery is no longer the last resort.
• Refer to the epileptologist any patient fail 2 AED.
THANK YOU