Pharmacoresistant epilepsy: Definition, presentation and the role of diagnosis

December 2, 2011

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# Disclosure

<table>
<thead>
<tr>
<th>Name of Commercial Interest</th>
<th>Type of Financial Relationship</th>
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<tr>
<td>BIAL</td>
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Learning Objectives

• Identify three features of the natural history and presentation of pharmaco-resistance that pose challenges to improving its recognition and treatment.

• Recognize that inadequate diagnostic accuracy of epilepsy, seizures, and their causes is a potential barrier to improving care.
What is pharmacoresistant epilepsy?

- Seizures are uncontrolled by medication
- Strictest sense:
  - Failure of all therapies – singly and in all possible combinations to control seizures.
    - J. Engel
- Currently:
  - >20 different AEDs available
Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies

*1 Patrick Kwan, †Alexis Arzimanoglou, ‡Anne T. Berg, §§Martin J. Brodie, ¶W. Allen Hauser, #²Gary Mathern, **Solomon L. Moshé, ††Emilio Perucca, ‡‡Samuel Wiebe, and §§§²Jacqueline French

Epilepsia, 2009

*Failure to control seizures fully
*of two appropriate AEDs
*used in informative trials
Assumptions and misunderstandings about pharmacoresistant epilepsy

- Pharmacoresistance is:
  - 1) apparent from onset
  - 2) the same in everyone
  - 3) stable over time
1. Pharmacoresistance is not always apparent from the start.


Early onset Encephalopathies

Nonsyndromic, focal
Remission before surgery and age at onset of epilepsy

% of age group

Duration of previous remission

- <5
- 5-
- 10-
- 15-
- 20-
- 30-
- 40-
- 1+ yrs
- 5+yrs
- 10+yrs

Berg et al. Neurology 2003
2. Pharmacoresistance varies in its presentation

- Relentless, multiple daily seizures
- A seizure or two a week
- Sz/month
- A seizure every few months
- 1-2 sz/year despite reasonable pharmacological treatment

3. Pharmacoresistance is NOT stable over time

Outcome after 2 informative trial failures, and 1+ additional trial

Berg et al., Ann Neurol, 2009
Repeated remissions and relapses are common even after 2 drug failures

Berg et al., Ann Neurol, 2009
Assumptions and misunderstandings about pharmacoresistant epilepsy

Pharmacoresistance is **NOT** always:

1) apparent from onset
2) the same in everyone
3) stable over time
Diagnosis

• Definition of pharmacoresistance requires **appropriate** drug for the epilepsy!

Accurate diagnosis is critical for determining “appropriateness” of an AED.
Hypothetical RCT for epilepsy

- 1200 patients with newly diagnosed epilepsy
- Randomly assigned to AED1, AED2, AED3

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AED1 (389)</th>
<th>AED2 (407)</th>
<th>AED3 (406)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>5.4y</td>
<td>5.3y</td>
<td>5.5y</td>
</tr>
<tr>
<td>Sex (%male)</td>
<td>52.3%</td>
<td>51.5%</td>
<td>53.0%</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year seizure-free</td>
<td>45%</td>
<td>20%</td>
<td>15%</td>
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Hypothetical RCT for epilepsy

- 1200 Infants and children with newly diagnosed epilepsy
- Randomly assigned to CBZ, ESM, or ACTH

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<tr>
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<td>51.5%</td>
<td>53.0%</td>
</tr>
<tr>
<td>West syndrome</td>
<td>2.5%</td>
<td>1.9%</td>
<td>2.2%</td>
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<tr>
<td>Childhood absence epilepsy</td>
<td>12.5%</td>
<td>10.9%</td>
<td>13.1%</td>
</tr>
<tr>
<td>Benign Rolandic epilepsy</td>
<td>9.8%</td>
<td>12.1%</td>
<td>10.5%</td>
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<tr>
<td>Dravet syndrome</td>
<td>0.5%</td>
<td>0.8%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>5.0%</td>
<td>4.3%</td>
<td>7.4%</td>
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<tr>
<td>Nonsyndromic focal epilepsy</td>
<td>55.6%</td>
<td>51.3%</td>
<td>54.8%</td>
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<tr>
<td>Other epilepsies</td>
<td>14.1%</td>
<td>18.7%</td>
<td>10.9%</td>
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Epilepsy is not a single disorder

• In children:
  – Dramatic differences in choice of treatment based upon clinical presentation and specific epilepsy diagnosis.

• In adults:
  – MTLE
  – ?????
• Very little epilepsy in the general population is “classic” TLE with HS

• Most epilepsies are inadequately characterized
  – Sloppy, imprecise terminology
    • Cryptogenic and symptomatic focal epilepsy
    • Complex and simple partial seizures
Explosion of new drugs in past decade

Brodie, Antiepileptic drug therapy: the story so far. Seizure, 2010

Fig. 1. Chronology of antiepileptic drug introduction over the past 150 years.
(2) Probability of success on N+1 drug after failing Nth drug

“Partial”
~55% to first or second drug
~80-85% eventually respond,

Schiller&Najjar, Neurology 2008
Could we do better?

• Is it really random dumb luck?
• What would we need to know to determine which drug might have the best chance for controlling seizures for a given patient?
Phenotyping garden variety focal epilepsies?

- Age at onset
- Specific underlying cause
  - specific genetic
  - Specific structural lesions
- Specific EEG patterns
- Details of seizure semiology
- Diurnal patterns of occurrence
- Triggers
Could better early diagnosis be the key?

• Spectacular advances
  – available treatments
  – diagnostic capabilities
    • Imaging
    • Neurophysiology
    • Genomics

• Not matched by spectacular advances in precision of epilepsy diagnoses for vast majority with “nonsyndromic” epilepsies.