Etiologies of refractory epilepsy and pseudo refractory epilepsy

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Refractory epilepsy

- **Terminology**: drug-resistant epilepsy (DRE)
  - pharmaco-resistant epilepsy (PRE)

- **Definition**
  - failure of adequate drug trials of 2 tolerated and appropriately chosen and used AED regimens to achieve seizure freedom (monoRx or polyRx)
  - seizure freedom
    1. a period of at least 12 months or
    2. a period that is at a minimum 3 times longer than the longest preintervention interseizure interval
Etiologies of refractory epilepsy

How to approach

- R/O pseudo refractory epilepsy

- True refractory epilepsy
  - Structural vs Genetic related
  - Pattern of epileptic and developmental progression
  - Disease biology
Pseudo refractory epilepsy

• Wrong diagnosis:
  Paroxysmal event: self-gratification, syncope, etc
  Psychogenic non epileptic seizure (PNES)
  Failure to identify an underlying causes e.g. metabolic illness

• Inappropriate treatment of epilepsy
  Incorrect AED selection:
  wrong drug for epilepsy type
  decreased efficacy of AED due to drug interaction
  Corrected AED but inappropriate dosage
  Corrected AED but wrong preparation
Pseudo refractory epilepsy

- Non-adherence to therapy
  - Poor compliance, unusual lifestyle, alcohol abuse
  - Intolerable adverse effects
  - Inadequate patient education
  - Prohibitive cost of medication
PNES

- Sudden alterations of behaviour that resemble epileptic seizures
- Psychogenic factors---causes of that problem
- Young children: PNES—prolonged episodes of unresponsiveness with reduction of spontaneous movement
- Older children+adult: PNES—excessive motor activity associated with impairment of consciousness
- Epileptic seizure and PNES can occur concomitantly
Table. Differences in Physical Manifestations of Psychogenic Nopileptic and Epileptic Seizures

<table>
<thead>
<tr>
<th>Factor</th>
<th>Psychogenic Nonepileptic Seizures</th>
<th>Epileptic Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Prolonged</td>
<td>Briefer (usually &lt; 5 min)</td>
</tr>
<tr>
<td>Clinical features during episode</td>
<td>Fluctuating</td>
<td>Stereotypic</td>
</tr>
<tr>
<td>Time of day</td>
<td>Usually during wakefulness in the presence of an audience</td>
<td>May occur in sleep whether or not anyone is present</td>
</tr>
<tr>
<td>Consciousness</td>
<td>Preserved even with generalized motor activity</td>
<td>Usually altered (exception is supplementary motor area seizures)</td>
</tr>
<tr>
<td>Onset</td>
<td>Gradual, with slow escalation in intensity</td>
<td>Abrupt</td>
</tr>
<tr>
<td>Head movements</td>
<td>More frequently side-to-side</td>
<td>Usually unilaterally turned, with staring expression</td>
</tr>
<tr>
<td>Extremity</td>
<td>Out-of-phase movements, unusual posturing</td>
<td>In-phase movements, rhythmic muscle contractions</td>
</tr>
<tr>
<td>Vocalizations</td>
<td>Emotional (crying) in the middle or end of episode</td>
<td>Cry at the onset of episode</td>
</tr>
<tr>
<td>Eyes</td>
<td>Closed during the episode</td>
<td>May be open during the episode</td>
</tr>
<tr>
<td>Pelvic thrusting</td>
<td>Forward direction</td>
<td>Retrograde direction</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Rare</td>
<td>May be present</td>
</tr>
<tr>
<td>Related injury</td>
<td>Inconsistent with fall</td>
<td>Consistent with fall</td>
</tr>
<tr>
<td>Tongue bite</td>
<td>Occasional (usually at the tip)</td>
<td>Common (at the side)</td>
</tr>
<tr>
<td>Postictal change</td>
<td>None or brief, even after prolonged generalized convulsive event</td>
<td>Prolonged, with confusion and exhaustion (although maybe absent after frontal lobe seizures)</td>
</tr>
<tr>
<td>Signs that favor PNES</td>
<td>Evidence from primary studies</td>
<td>Sensitivity (%) for PNES</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Long duration</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Fluctuating course</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Asynchronous movements</td>
<td>Good (frontal lobe partial seizures excluded)</td>
<td>47–88 (patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44–96 (events)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9–56 (patients)</td>
</tr>
<tr>
<td>Pelvic thrusting</td>
<td>Good (frontal lobe partial seizures excluded)</td>
<td>1–31 (events)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.4–44 (patients)</td>
</tr>
<tr>
<td>Side to side head or body movement</td>
<td>Good (convulsive events only)</td>
<td>25–63 (events)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15–36 (patients)</td>
</tr>
<tr>
<td>Closed eyes</td>
<td>Good</td>
<td>34–88 (events)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>52–96 (patients)</td>
</tr>
<tr>
<td>Ictal crying</td>
<td>Good</td>
<td>13–14 (events)</td>
</tr>
<tr>
<td>Memory recall</td>
<td>Good</td>
<td>3.7–37 (patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63 (events)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>77–88 (patients)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs that favor ES</th>
<th>Evidence from primary studies</th>
<th>Sensitivity for ES</th>
<th>Specificity for ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurrence from EEG-confirmed sleep</td>
<td>Good</td>
<td>31–59 (events)</td>
<td>100</td>
</tr>
<tr>
<td>Postictal confusion</td>
<td>Good</td>
<td>61–100 (events)</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>67 (patients)</td>
<td>84</td>
</tr>
<tr>
<td>Stertorous breathing</td>
<td>Good (convulsive events only)</td>
<td>61–91 (events)</td>
<td>100</td>
</tr>
<tr>
<td>Other signs</td>
<td>Evidence from primary studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gradual onset</td>
<td>Insufficient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonstereotyped events</td>
<td>Insufficient</td>
<td></td>
<td></td>
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<tr>
<td>Flailing or thrashing movements</td>
<td>Insufficient</td>
<td></td>
<td></td>
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<tr>
<td>Opisthotonus “arc en cercle”</td>
<td>Insufficient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tongue biting</td>
<td>Insufficient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Insufficient</td>
<td></td>
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</tbody>
</table>
The importance of refractory epilepsy

Increased risks of

- Premature death, SUDEP
- Injuries
- Psychosocial dysfunction
- Reduced quality of life
Etiologies of refractory epilepsy

How to approach

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- True refractory epilepsy
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  - Disease biology
Etiologies of refractory epilepsy

**Structural/metabolic causes:**
- Congenital: FCD, brain malformation, neurocutaneous syndrome, Otahara, metabolic, etc
- Acquired: anoxia, post-infection, tumor, traumatic, autoimmune etc

**Genetic related causes:**
- Epileptic syndromes: Dravet etc
- Syndrome associated: Waardenberg etc
- Chromosomal abnormality: Ring chr 20 etc
- *Genetic related of multidrug resistance*
Etiologies of refractory epilepsy

Pattern of epileptic and developmental progression

- Epileptic encephalopathy:
  - Otahara syndrome
  - West syndrome
  - Dravet syndrome
  - LGS
  - LKS
  - etc.
Etiologies of refractory epilepsy

Disease biology
- Etiology of sz (eg. progressive epilepsy syndrome; LGS, myoclonic encephalopathy)
- Severity of the disease
- Abnormal network plasticity
- Ion channelopathy
- Reactive autoimmunity
- Impaired AED penetration
- Altered drug targets/receptors
- Disrupted integrity of BBB
Clinical predictors that have been associated with DRE

1. Number of seizures per time before Rx initiation
2. Long Hx of poor seizure control
3. Early onset of seizures
4. More than one seizure type
5. Multiple seizures after Rx initiation
6. Remote symptomatic etiology
7. Certain structural abnormalities eg. CD, HS
8. Certain EEG abnormalities
9. Mental retardation
10. Psychiatric comorbidity
11. Abnormal neurological examination
12. Hx of status epilepticus

*Andreas VA: epileptology 1 (2013) 38-42*
Hypotheses mechanisms of DRE

1. Drug transporter hypothesis
2. Target hypothesis
3. Network hypothesis
4. Gene variant hypothesis
5. Severity hypothesis

Nature reviews drug discovery 2013
Hypothesized biologic mechanism of DRE