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 Nonepileptic and Epileptic Seizures**

Factor	Psychogenic Nonepileptic Seizures	Epileptic Seizures
Duration	Prolonged	Briefer (usually <5 min)
Clinical features during episode	Fluctuating	Stereotypic
Time of day	Usually during wakefulness in the presence of an audience	May occur in sleep whether or not anyone is present
Consciousness	Preserved even with generalized motor activity	Usually altered (exception is supplementary motor area seizures)
Onset	Gradual, with slow escalation in intensity	Abrupt
Head movements	More frequently side-to-side	Usually unilaterally turned, with staring expression
Extremity	Out-of-phase movements, unusual posturing	In-phase movements, rhythmic muscle contractions
Vocalizations	Emotional (crying) in the middle or end of episode	Cry at the onset of episode
Eyes	Closed during the episode	May be open during the episode
Pelvic thrusting	Forward direction	Retrograde direction
Incontinence	Rare	May be present
Related injury	Inconsistent with fall	Consistent with fall
Tongue bite	Occasional (usually at the tip)	Common (at the side)
Postictal change	None or brief, even after prolonged generalized convulsive event	Prolonged, with confusion and exhaustion (although maybe absent after frontal lobe seizures)

Table 1. Summary of evidence that supports the signs used to distinguish between psychogenic nonepileptic seizures (PNES) and epileptic seizures (ES)*

Signs that favor PNES	Evidence from primary studies	Sensitivity (%) for PNES	Specificity (%) for PNES
Long duration	Good	–	–
Fluctuating course	Good	69 (events)	96
Asynchronous movements	Good (frontal lobe partial seizures excluded)	47–88 (patients)	96–100
		44–96 (events)	93–96
		9–56 (patients)	93–100
Pelvic thrusting	Good (frontal lobe partial seizures excluded)	1–31 (events)	96–100
		7.4–44 (patients)	92–100
Side to side head or body movement	Good (convulsive events only)	25–63 (events)	96–100
		15–36 (patients)	92–100
Closed eyes	Good	34–88 (events)	74–100
		52–96 (patients)	97
Ictal crying	Good	13–14 (events)	100
		3.7–37 (patients)	100
Memory recall	Good	63 (events)	96
		77–88 (patients)	90
Signs that favor ES	**Evidence from primary studies**	**Sensitivity for ES**	**Specificity for ES**
Occurrence from EEG-confirmed sleep	Good	31–59 (events)	100
		–	–
Postictal confusion	Good	61–100 (events)	88
		67 (patients)	84
Stertorous breathing	Good (convulsive events only)	61–91 (events)	100
		–	–
Other signs	**Evidence from primary studies**		
Gradual onset	Insufficient		
Nonstereotyped events	Insufficient		
Flailing or thrashing movements	Insufficient		
Opisthotonus "arc en cercle"	Insufficient		
Tongue biting	Insufficient		
Urinary incontinence	Insufficient		

WC LaFranceJr et al. Epilepsia 2013

The importance of refractory epilepsy

Increased risks of

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

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Etiologies of refractory epilepsy

Structural/metabolic causes:

- Congenital : FCD, brain malformation, neuro-cutaneous 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

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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

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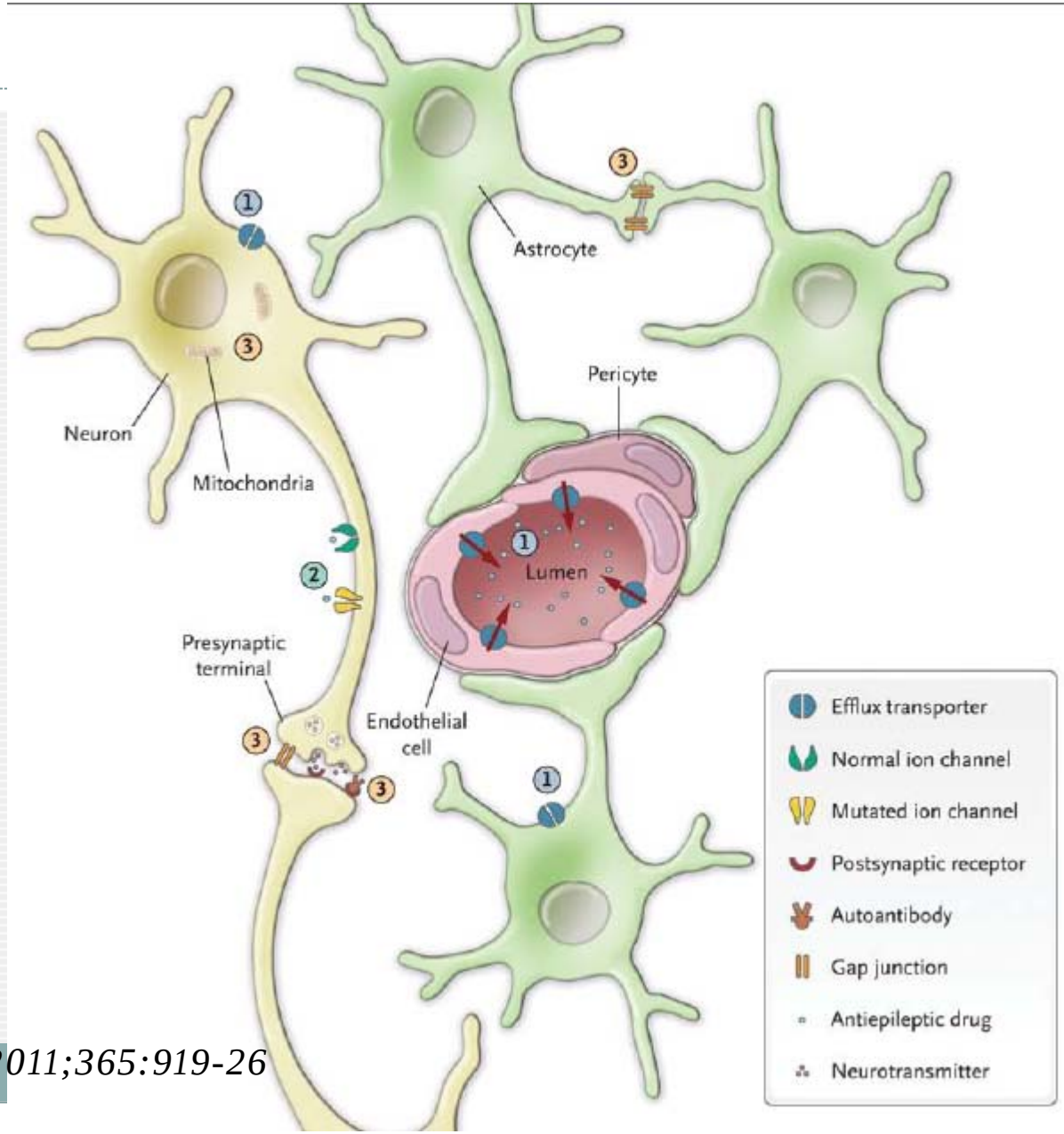
Hypotheses mechanisms of DRE

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



N Engl J Med 2011;365:919-26