Secondary Epileptogenesis

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Secondary Epileptogenesis

A process by which an eventually irreversible, secondary epileptic focus is established in an area remote from the primary epileptic focus, in a homotopic or ipsilaterally connected location, due to repeated invasion by seizures and IEDs.

The concept of secondary epileptogenesis does not encompass:

• development of epilepsy following early life insults eg. mTLE following PFC
• worsening of epilepsy due to locally recurrent seizures
• detrimental, non-seizure effects of epilepsy eg. cognition, behaviour, MRI
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Scope

- experimental models of 2° epileptogenesis in animals
  - limbic kindling
  - “mirror focus”

- examples of 2° epileptogenesis in human focal epilepsy
  - “mirror foci” in neocortical tumoural epilepsy
  - “mirror foci” in mTLE
  - remote ipsilateral foci eg. occipitotemporal, frontotemporal
  - symptomatic generalised epilepsy in HH and FCD

- pathophysiological basis of 2° epileptogenesis

- practical implications of 2° epileptogenesis
Animal Models – Mirror Focus

• create a 1° cortical focus with a single freezing or chemical lesion
  → 1° focus exhibits IEDs and seizures
  → IEDs and seizures propagate to contralateral homotopic cortex
  → IEDs and seizures arise independently in the “mirror” 2° focus

  Morrell F. J Clin Neurophysiol 1989

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• intravenous methohexital (Brevital®) suppression of IEDs:
  - early on, MHT suppresses the $2^o$ focus well before the $1^o$ focus
  - later on, the $2^o$ focus is resistant to MHT suppression

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  - later on, the 2<sup>o</sup> focus is resistant to MHT suppression
- resection or disconnection of the 1<sup>o</sup> focus:
  - early on, leads to immediate or gradual remission of the 2<sup>o</sup> focus
  - later on, leads to persistent IEDs and seizures from the 2<sup>o</sup> focus
Animal Models – Mirror Focus

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• resection or disconnection of the 1º focus:
  - early on, leads to immediate or gradual remission of the 2º focus
  - later on, leads to persistent IEDs and seizures from the 2º focus

• the effectiveness and latency of mirror focus development depends on:
  - species studied
  - synaptic connectivity of the 1º focus (eg. not in precentral gyrus)

Stages of 2º Epileptogenesis (Morrell)

1st stage = dependent stage of 2º epileptogenesis
• IEDs occur synchronously with the 1º focus only
• removal of 1º focus leads to immediate cessation of IEDs

2nd stage = intermediate stage of 2º epileptogenesis
• ↑ IEDs and occasional seizures occur independent of the 1º focus
• removal of 1º focus leads to delayed cessation of seizures and IEDs

3rd stage = independent stage of 2º epileptogenesis
• IEDs and ↑ seizures occur independently from the 1º focus
• removal of 1º focus followed by persistence of seizures and IEDs
Tumour-related, Neocortical Epilepsy

Morrell F. J Clin Neurophysiol 1989;6
- 116 operated patients with tumoural, neocortical epilepsy (MNI & Chicago)
- bilateral IEDs 21-38%
- independent contralateral seizures in 15%
- 2/3 gradual postop seizure remission, 1/3 seizure persistence
- persistent seizures in patients with MHT-resistant focus

Lim SH et al. Arch Neurol 1991;48
- 60 TLE patients undergoing ATL (Cleveland Clinic)
- 30 with unilateral IEDs and 30 with bilateral IEDs
- tumours (? localised pathology) associated with bilateral IEDs
- prolonged FC/encephalitis (? diffuse pathology) associated with unilateral IEDs

Gilmore R et al. Epilepsia 1994;35
- 22 patients with tumoural TLE undergoing surgery (Cleveland Clinic)
- 7 with mirror foci and 15 without mirror foci
- no difference in seizure onset, epilepsy duration, seizure frequency or outcome

Bilateral EEG in mTLE

bilateral interictal epileptiform discharges (IEDs)

contralateral seizure propagation and independent bilateral seizures
Bilateral EEG and ATL Outcome in mTLE -1

• 59 TLE patients, bilateral subdural EEG monitoring
• seizure-freedom in 87% with unilateral seizures & IEDs, 40-56% with unilateral seizures but bilateral IEDs, and 13% with bilateral seizures

Lee et al. Epilepsia 2000;41
• depth EEG recordings of seizures in TLE patients
• seizure freedom in 84% with unilateral seizures and 47% with contralateral seizure propagation

Schulz R et al. Epilepsia 2000;41
• 58 TLE patients with MTS or no lesion
• seizure freedom in 89% with unilateral seizures & IEDs, 74% with contralateral IEDs or seizure propagation, and 33% with contralateral IEDs and seizure propagation

Bilateral EEG and ATL Outcome in mTLE -2

Malow et al. Epilepsia 1999;40
• bitemporal IEDs associated with poor postop outcome if normal MRI
• good outcome with bitemporal IEDs if unilateral hippocampal abnormality

Lee et al. ESA 2006 (poster 556)
• 83 pts with refractory, lesional TLE
• unilateral lesions (HS 55, FTL 14, other 14)
• lesionectomy or lobectomy (2-6 yrs follow-up)
• 48% patients seizure free
• no negative effect on seizure outcome of:
  - contralateral IEDs
  - contralateral seizure propagation
Epilepsy Duration in mTLE

Janszky J et al. Seizure 2003;12
- 243 patients with mTLE and unilateral HS
- 2/3 unilateral IEDs, 1/3 bilateral IEDs
- no difference in epilepsy duration
- late-onset TLE assoc with bilateral IEDs

McIntosh AM et al. Brain 2004;127
- 325 patients with mTLE underwent ATL with mean follow-up 9.6 yrs
- 48% seizure free at 5 years
- after adjustment for preoperative pathology, no effect of
  - age at seizure onset
  - age at surgery
  - duration of epilepsy

Human Examples of Mirror Foci

- conflicting evidence in humans and few proven cases
- clinical research confounded by:
  - heterogeneity of epilepsy samples studied and small numbers
  - aetiologies with potential for bilateral pathology
  - insensitivity and unreliability of scalp EEG
  - short follow-up in seizure outcome studies
- lack of correlation between markers of 2° epileptogenesis (bilateral IEDs/seizures, postop sz) and expected biological factors (duration of epilepsy, lifetime seizures)

Frank Morrell
- 2° epileptogenesis altered by AEDs in humans
- good outcomes in mirror foci cases = stage 2 (intermediate)
gelastic seizures  complex partial seizures  tonic, atonic, spasms

Hypothalamic hamartoma


HH and Tonic Seizures – sEEG studies

Evolution and Postoperative Resolution of Seizures in HH

Harvey et al, Epileptic Disorders 2003

before HH resection
after HH resection

Freeman et al, Neurology 2003
EEG improvement after HH surgery

mean SW% for SGE patients (n=14)

<table>
<thead>
<tr>
<th>Awake</th>
<th>Asleep</th>
<th>Total</th>
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<tbody>
<tr>
<td>17%</td>
<td>4%</td>
<td>19%</td>
</tr>
<tr>
<td>48%</td>
<td>4%</td>
<td>4%</td>
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<tr>
<td>32%</td>
<td>12%</td>
<td>12%</td>
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</tbody>
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Freeman et al, Neurology 2003

15 yrs old boy: LGS with tonic seizures, intellectual disability and left frontal dysplasia
gradually became seizure free (4 years) with alerting and EEG normalisation

7 yrs girl: LGS with tonic seizures and spasms, developmental regression and slow SW
SGE and Focal Cerebral Lesions

- not (necessarily) diffuse (occult) cortical dysplasia
- not irreversible secondary damage from seizures
- tonic seizures are not secondarily generalised partial sz
- GSW on EEG is not secondary bilateral synchrony
- evolves over time in an age-dependent manner
- may remit with surgery, AEDs or spontaneously
- immediately after surgery, seizures and EEG disturbances may persist (in sleep) and then run down
- a potentially-reversible, generalised functional disturbance overlaid on a focal seizure disorder
SGE and Focal Cerebral Lesions

? generalised form of secondary epileptogenesis via a complex cortical-subcortical interaction
  ie. maladaptive changes in response (reactive) to seizure focus

Implications of secondary Epileptogenesis

? AEDs should ideally have anti-epileptic effects
? counsel about diminished surgery outcome if contralateral IEDs or seizures
? need to act urgently in someone who develops a mirror or remote EEG focus
  or
? it probably exists, but has no practical implications, as you can't tell the difference between stages 2 and 3!

Stage 2
or
Stage 3
reversible or irreversible
Secondary Epileptogenesis

A process by which an eventually irreversible, secondary epileptic focus is established in an area remote from the primary epileptic focus, in a homotopic or ipsilaterally connected location, due to repeated invasion by seizures and IEDs.

A form of maladaptive plasticity.


Frank Morrell
1926-1996