What do we know about prognosis and natural course of epilepsies?

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The Thai Red Cross Society
First unprovoked seizure
Untreated epilepsy
Treated epilepsy
Medically intractable epilepsy with surgeries
Natural course and prognosis of first unprovoked seizure
Early prognosis:
Risk of recurrence after first unprovoked seizure

✓ Pooled estimate of 2 year recurrence risk = 42% (30-50%)

Berg AT and Shinnar S Neurology 1991
Hart YM et al; The Lancet 1990
Risk of recurrence

After first, second and third seizure

- Patients with first seizure: 33%
- Patients with second seizure: 73%
- Patients with third seizure: 76%

Etiology

- Remote symptomatic (n = 26): 87%
- Idiopathic (n = 37): 64%

Hauser WA et.al; NEJM 1998
What are the predictors of recurrence?

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Pooled RR of recurrence</th>
<th>Pooled risk of 2 year recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal neurological status</td>
<td>1.8</td>
<td>57</td>
</tr>
<tr>
<td>Normal EEG</td>
<td>2.0</td>
<td>58</td>
</tr>
<tr>
<td>Epileptiform abnormalities in EEG</td>
<td>1.2</td>
<td>27</td>
</tr>
<tr>
<td>Non-epileptiform abnormalities in EEG</td>
<td>1.3</td>
<td>37</td>
</tr>
<tr>
<td>Aetiology and EEG combined</td>
<td>2.0</td>
<td>58</td>
</tr>
<tr>
<td>Idiopathic + normal EEG</td>
<td>1.9</td>
<td>48</td>
</tr>
<tr>
<td>Idiopathic + abnormal EEG</td>
<td>1.9</td>
<td>48</td>
</tr>
<tr>
<td>Remote symptomatic + normal EEG</td>
<td>1.9</td>
<td>48</td>
</tr>
<tr>
<td>Remote symptomatic + abnormal EEG</td>
<td>1.4</td>
<td>65</td>
</tr>
</tbody>
</table>

EEG, electroencephalogram; RR, relative risk.

Camfield P and Camfield C Epilepsia 2000
Immediate vs deferred treatment after a first unprovoked seizure

- 2 yr-remission: 69% vs 61%
  - At 3 yrs: 1-3 yrs sz remission: 74% vs 71%
  - At 5 yrs: 3-5 yr sz remission: 76% vs 77%

“Immediate antiepileptic drug treatment reduces the occurrence of seizures in the next 1–2 years, but does not affect long-term remission in individuals with single or infrequent seizures”

Marson A et.al The Lancet 2005
Immediate vs deferred treatment after a first unprovoked seizure

**FIR.S.T. (First Seizure Trial) studies**

- Treatment of the first seizure increased the probability of a 2-year remission in the first 3 years; however, the difference disappeared after a longer period of follow-up (only patients with GTCs were included)

*Maurizio AL et.al Neurology*
Prediction of risk of seizure recurrence

<table>
<thead>
<tr>
<th>Starting value</th>
<th>Prognostic Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>One seizure prior to presentation</td>
<td>0</td>
</tr>
<tr>
<td>Two or three seizures prior to presentation</td>
<td>1</td>
</tr>
<tr>
<td>Four or more seizures prior to presentation</td>
<td>2</td>
</tr>
<tr>
<td>Add if present</td>
<td></td>
</tr>
<tr>
<td>Neurological disorder or deficit, learning disability, or developmental delay</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal EEG</td>
<td>1</td>
</tr>
<tr>
<td>Risk classification group for seizure recurrence*</td>
<td>Final score</td>
</tr>
<tr>
<td>Low risk</td>
<td>0</td>
</tr>
<tr>
<td>Medium risk</td>
<td>1</td>
</tr>
<tr>
<td>High risk</td>
<td>2-4</td>
</tr>
</tbody>
</table>

*See table 3 for probabilities of no seize recurrence at specific time points for each of these subgroups.

Table 4: Prognostic index, with integer values

"There is little benefit to immediate treatment in patients at low risk of seizure recurrence, but potentially worthwhile benefits are seen in those at medium and high risk"

Kim LG et.al The Lancet 2006
Natural course and prognosis of untreated epilepsies
Introduction

- The course of disorders from onset to resolution, without interventions (Last, 1988)

- Evidence-based treatments with proven efficacy alter the natural course of disorders

- Prospective studies in untreated patients are thus not possible.
Effect of duration and number of seizure prior to treatment

- Gower's observation and Reynolds EH studies pointed out that the longer the history of epilepsy the worse the longer term prognosis.

241 adults with newly diagnosed epilepsy treated with one drug

Gowers WR 1881
Reynolds EH; BMJ 1995
Reynolds EH et.al; Epilepsia 1989
Effect of number of seizure prior to treatment

135 adult patients with partial seizure or GTCs
- Treated with either PB or PHT
- Primary outcome: 2-year seizure freedom

Group I: good compliance coupled with lifetime total of ≤ 30 GTCs
Group II: poor compliance and lifetime total ≥ 30 GTCs

Mani et al.; Lancet 2001
The effects of AEDs on long-lasting untreated epilepsy

- A study in Kenya (Lancet, 1991): a finding that does not support the suggestion that the disorder becomes intractable if not treated early.
- Neither length of history of epilepsy nor number of seizures before treatment influenced effect of therapy.
- Similar to other studies in developing countries (Malawi and Ecuador).

302 pts (152 CBZ; 150 PB)

249 (82%) completed 12-mo study

- Seizure free 52%; 54%
- Decreased frequency 29%; 23%
- No change in seizure frequency 13%; 15%
- Increased frequency 6%; 8%
- Number completing trial < 5 years 116 > 5 year 133 (52%)
- Good 80% 78%
- No change 16% 13%
- Worse 4% 9%

** p > 0.05

Feksi AT et.al; Lancet 1991
Watts AE; Br Med J 1989
Placencia et.al; JNNP 1994
Natural course and prognosis of treated epilepsies
Effectiveness of AEDs

- 470 patients with newly-diagnosed epilepsy
- Seizure-free for at least 1 year
  - 1st drug: 47%
  - 2nd drug mono: 13%
  - 3rd drug mono: 1%
  - Two drugs: 3%

Medically controlled: 64%
Medically refractory: 36%

Table 2: Success of Antiepileptic-Drug Regimens in 470 Patients with Previously Untreated Epilepsy.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to first drug</td>
<td>222 (47)</td>
</tr>
<tr>
<td>Seizure-free during continued therapy with first drug</td>
<td>207 (44)</td>
</tr>
<tr>
<td>Remained seizure-free after discontinuation of first drug</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Response to second drug</td>
<td>61 (13)</td>
</tr>
<tr>
<td>Seizure-free during monotherapy with second drug</td>
<td>41 (9)</td>
</tr>
<tr>
<td>Remained seizure-free after discontinuation of second drug</td>
<td>20 (4)</td>
</tr>
<tr>
<td>Response to third drug or multiple drugs</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Seizure-free during monotherapy with third drug</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Seizure-free during therapy with two drugs</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>301 (64)</td>
</tr>
</tbody>
</table>

Kwan P and Brodie M; Epilepsia 2001
Medically controlled: 68%

Medically refractory: 32%

<table>
<thead>
<tr>
<th>Drug regimens</th>
<th>No. of patients</th>
<th>Seizure-free on monotherapy</th>
<th>Seizure-free on combination</th>
<th>Total no. seizure-free</th>
<th>% of cohort seizure-free</th>
<th>% Seizure-free on regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>1,098</td>
<td>543</td>
<td>0</td>
<td>543</td>
<td>49.5</td>
<td>49.5</td>
</tr>
<tr>
<td>Second</td>
<td>398</td>
<td>101</td>
<td>45</td>
<td>146</td>
<td>13.3</td>
<td>36.7</td>
</tr>
<tr>
<td>Third</td>
<td>168</td>
<td>26</td>
<td>15</td>
<td>41</td>
<td>3.7</td>
<td>24.4</td>
</tr>
<tr>
<td>Fourth</td>
<td>68</td>
<td>6</td>
<td>5</td>
<td>11</td>
<td>1.0</td>
<td>16.2</td>
</tr>
<tr>
<td>Fifth</td>
<td>32</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>0.4</td>
<td>12.5</td>
</tr>
<tr>
<td>Sixth</td>
<td>16</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0.2</td>
<td>12.5</td>
</tr>
<tr>
<td>Seventh</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0.2</td>
<td>22.2</td>
</tr>
<tr>
<td>Eighth</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Ninth</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Despite the introduction of more than 15 new AEDs (since 1985), there is limited evidence endorsing improved outcomes in the common adult epilepsies over the past 30 years.

Based on two large studies by the same group, there has been slightly increased rate of seizure freedom from 64% to 68%.

Loscher W. and Schmidt D; Epilepsia 2011
Late prognosis

- Based on 3 longitudinal community-based studies with long-term follow up
  - Mayo Clinic Record linkage study (US)
  - Tonbridge study (UK)
  - Turku study (Finland) (childhood-onset epilepsy)
Mayo clinic study (20 years follow up)

At 10 years 65% seizure remission
At 20 years 76%

- 475 pts followed at least 5 yrs
- 141 pts > 20 yrs

Annegers et al; Epilepsia 1979
Mayo clinic study

Age onset < 10 yrs: 75% remission at 10 yrs

Higher remission: generalized-onset seizure diagnosed < 10 yrs

Lower remission: CPS with adult onset
Tonbridge study (15 years follow up)

About one fifth (20%) of the patients continued to have seizure (chronic epilepsy)

Goodridge and Shorvon; BMJ 1983
Tonbridge study

- At 5 years after the first seizure of those whose epilepsy was still active, only 21% achieved subsequent terminal remission as compared with 96% of those who were already in remission.

“the longer seizure continues to occur, the lower the probability for subsequent remission”
The more number of seizure in the 6 months after the first seizure, the lesser is the chance of long-term remission.

Figure 2 NGPSE: the influence of seizure density on long-term remission. The percentage of patients achieving remission in those who had experienced one (dashed line), two (solid line), five (dotted line), or 10 (dashed and dotted line) seizures in the period from the index seizure to 6 months.
Turku study (37 years follow up)

- Seizure before the age of 16 years

- 67% achieved terminal remission (5-year seizure freedom at the end of follow up)
- 19% drug resistant
- 19% entered terminal remission after a relapse

Sillanpaa M and Schmidt D; Brain 2006
Conclusion

- 2/3 of the patients (58-65%) achieved 5-year cumulative terminal remission at 7-10 years follow up

- 3/4 of the patients (67-78%) with childhood-onset epilepsy achieved 3-5 year remission at 12-37 years follow up

- Neurological deficits, age onset, seizure type, number of early seizure influence on long-term remission rate
Natural course and prognosis of medically intractable epilepsy with surgeries
The patients in the surgical group had fewer seizures impairing awareness and a significantly better quality of life (P<0.001 for both comparisons) than the patients in the medical group.

Wiebe S et al; NEJM 2001
Long-term (>5 yrs) median seizure freedom rate (Engel I) after ATL was 65% (19 studies)
Percent seizure free

- Frontal: 27%
- Grouped extratemporal: 34%
- Callosotomy: 35%
- Parietal-occipital: 46%
- Temporal and extratemporal: 59%
- Hemispherectomy: 61%
- Temporal: 66%

Tellez-Zenteno JF et al; Brain 2005
Weihe S and Jette N; Curr Opin Neurol 2012
The outcome of surgical treatment in patients with epilepsy

Wiebe S and Jette N; Nat Rev Neurol 2012
Referred cases at CCEC

- Continuing seizures due to inadequate AEDs adjustment
- Medically intractable TLE
- Difficult surgical cases requiring extensive investigations
Seizure outcome of the new referred cases at CCEC during year 2554-2557

Total N = 419

- Seizure freedom: 35%
- Seizure reduction > 50%: 19%
- Not improved: 46%
Long-term courses of Juvenile myoclonic epilepsy (JME)
JME

- Original report on JME, published in 1957, Janz and Christian highlighted the rarity of spontaneous remission, as well as the high risk of relapse after AED discontinuation.
- Further studies with follow-up periods not longer than 5 years confirmed the initial observation.
- Based on 3 recent population-based studies with long-term follow up varying from 25 to 63 years after epilepsy onset:
  - 78%, 67.7%, and 59.1% achieved seizure remission
  - 25%, 28.6%, and 28.2% were seizure-free off medication for at least the last 5 years

Camfield CS and Camfield PR; Neurology 2009
Geithner J et.al; Epilepsia 2012
Senf P et.al; Neurology 2013
Predictors for seizure recurrence

- Additional absence seizure at onset of JME
- GTCs preceded by bilateral myoclonic seizures
- A long duration of epilepsy with unsuccessful treatment
- AED polytherapy
- Occurrence of photoparoxysmal responses
Thank you for your attention