The epileptic encephalopathies

concepts & prognostic factors

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Epilepsia 1966;7: 139-179

ILAE Commission Report

A Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy: Report of the ILAE Task Force on Classification and Terminology

Jerome Engel, Jr.

Epileptic encephalopathy: A condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function. (new concept)
Focal lesional epilepsy
   *Eg hypothalamic hamartoma, hemimegalencephaly, tuberous sclerosis,*

- West syndrome
- Ohtahara syndrome
- Early myoclonic encephalopathy
- Migrating focal seizures of infancy
- Dravet syndrome
- Lennox Gastaut syndrome
- LKS/ CSWS
- Epilepsy with myoclonic atonic seizures
- BECTS

- Rasmussen Syndrome
Transitory Cognitive Impairment (TCI)

- Short impairment of cognitive function during interictal discharges (ID)
- Interaction of cognition and ID are bi-directional, complex and both material and side specific

Aarts et al 1984, Shewmon & Ervin, 1988, Binnie 2003
**Effect of epilepsy**

**Cognitive deficits progress over time**

Longitudinal study of a cohort with epilepsy onset < 3 years

<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline, Mean (SE)</th>
<th>1 Year, Mean (SE)</th>
<th>2 Years, Mean (SE)</th>
<th>3 Years, Mean (SE)</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>92.0 (1.5)</td>
<td>86.6 (2.0)</td>
<td>82.9 (2.4)</td>
<td>81.5 (2.7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Communication</td>
<td>93.4 (1.5)</td>
<td>90.4 (2.0)</td>
<td>87.2 (2.0)</td>
<td>85.2 (2.3)</td>
<td>.0003</td>
</tr>
<tr>
<td>Daily Living</td>
<td>89.6 (1.4)</td>
<td>79.0 (1.6)</td>
<td>76.5 (2.0)</td>
<td>74.6 (2.4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Motor</td>
<td>94.4 (1.7)</td>
<td>90.0 (2.2)</td>
<td>83.1 (2.5)</td>
<td>80.5 (3.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Social</td>
<td>96.1 (1.7)</td>
<td>92.7 (2.0)</td>
<td>90.0 (2.2)</td>
<td>88.8 (2.4)</td>
<td>.0015</td>
</tr>
</tbody>
</table>

*Berg et al Pediatrics 2004;114: 645-650*

Longitudinal study to 8-9 years following seizure onset <8 years

*Dichotomous IQ indicator strongly correlated with age at onset in pharmacoresistant group (p<0.0001), not pharmacoresponsive group (p=0.61)*

*Berg et al Neurology 2012;79:1384-1391*
‘Epileptic Encephalopathy’

‘the epileptic activity itself contributes to cognitive and behavioral impairments beyond that expected from the underlying pathology alone (e.g. cortical malformation)’

ILAE 2010
‘West Syndrome’

– *Infantile Spasms*
– *Hypsarrhythmia*
– *Developmental plateau*

85% developmental compromise, 60% ongoing seizures

Improved outcome related to short treatment lag, prompt response to treatment & shorter duration of hypsarrhythmia
Continuous spike wave of slow sleep
Treatment & outcome in ESES

- N=32
- Prospective treatment with sodium valproate+/- ethosuximide, benzodiazepine or steroid
- Statistically significant difference in mean IQ in drug responders cf nonresponders mean IQ 92 & 65 respectively
Loddenkemper et al Neurosurgery 2009;64:328-337

- 8 patients (7 infarct, 1 malformation)
- 6 hemispherectomy, 2 lobar/multilobar resection
- All resolution of ESES
- 6 seizure free following surgery
But not all due to epileptiform activity...

- Some disorders developmental delay evident prior to presentation with seizures *eg chromosomal abnormalities*

Angelmans syndrome

- > 80% of individuals with Angelmans
  - 75% < 3 yrs
- Generalised seizure types
- Nonconvulsive status epilepticus
But not all due to epileptiform activity...

- Others developmental slowing or regression occurs when epileptiform activity not frequent \(\text{eg Dravet syndrome}\)
  - Suggests \textit{both} a developmental and epileptic component
  - \textit{Both} likely secondary to underlying \textit{SCN1A} mutation

- 81 examinations in 67 children
- no loss of abilities;
- Cognitive outcome is related to epilepsy course and seizure characteristics
- \textit{myoclonia and focal seizures associated with a lower QD/IQ level after 3 years}
- \textit{SCN1A} mutation exhibit worse psychomotor course than non
Dravet syndrome—epileptic encephalopathy?

*Catarino et al Brain* 2011 [eprint 29 June]

- 22 adult cases – oldest 60 years
- Neurological deterioration occurred throughout life
- 7 had drug changes following diagnosis
- 3 meaningful follow-up – 2 improvement in cognition, one spontaneous language
- PM no consistent cerebral structural changes, cell loss or neurodegeneration
Dravet syndrome– epileptic encephalopathy?

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• In others outcome remains poor even though seizures stop eg KCNQ2 encephalopathy

  KCNQ2 cause of benign familial neonatal seizures
  Recognised as cause of more severe neonatal onset epilepsy
  • Tonic seizures
  • Suppression burst on EEG

  Good seizure control with sodium channel blockers, poor neurodevelopmental outcome, movement disorder
  • ?improved outcome with early prompt treatment

It's not all the epilepsy – but may have an impact
Where both delayed development and frequent epileptiform abnormalities suggest Developmental and/or Epileptic Encephalopathy.

Scheffer et al 2017 Epilepsia in press
Developmental and/or Epileptic Encephalopathy

- **Developmental encephalopathy**
  - *May begin in utero*
  - *Post birth*

- **Epileptic encephalopathy**
  - *Can occur at any age, any syndrome*
  - *May be remediable component – right vs wrong AED*

- Move towards *GENE* encephalopathy
  - *eg. CDKL5 encephalopathy, SCN2A encephalopathy*
  - *? Immune encephalopathies*