Early Onset Epilepsy: Epidemiology and Syndrome Diagnosis

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Epilepsy in Infancy in a population setting

- How common is it?
- How commonly are epilepsy syndrome diagnoses made?
- Which aetiologies are identified?
- Outcomes
Age specific incidence of unprovoked seizures and epilepsy

Olafsson et al, Lancet Neurology 2005; 4:627-34
Incidence of epilepsy onset < 12 months

Age specific incidence: < 1 year / 100.000 / year (n)

*asceraiment adjusted
North London Epilepsy in Infancy Study
Eltze et al; Epilepsia. 2013 Mar;54(3):437-45

- Hospital and Community based Paediatricians
  - monthly postal survey
  - telephone hot line

- Inclusion criteria:
  - Children age 4 weeks - 24 months
  - recurrent unprovoked seizures

- 57 enrolled over 13 months period

- Incidence (per 100,000 children < 2 years/year):
  - crude: 53.6 (CI 95% 41.4 – 69.5)
  - ascertainment adjusted: 70.1 (95% CI 56.3 – 88.5)

Other studies incidence onset under 2 years/100,000/year:
Nova Scotia, Canada [Camfield et al 1996]: 81 (95% CI 67-93)
UK 1958 National Child Development Study Cohort: 61 (95% CI 39-95) [Kurtz et al 1998]
North London Epilepsy in Infancy Study

High risk of epilepsy in the first year of life

Risk ratio for epilepsy < 12m versus 12-24m: 2.33 (95% CI [1.44, 3.76]; p< 0.005

Eltze et al; Epilepsia. 2013 Mar;54(3):437-45
Other studies

Wirrel et al 2011
Rochester Epidemiology Project

Camfield et al, 1996; Kurtz et al, 1998
Ethnicity and Incidence of Epilepsy <= 2 years
Eltze et al; Epilepsia. 2013 Mar;54(3):437-45

Ethnic composition – population in North London

- White: 55,267 (57%)
- Asian: 12,932 (13%)
- Black: 17,757 (18%)
- Mixed: 2,534 (3%)
- Other: 9,051 (9%)

North London Epilepsy in Infancy Cohort

- White: 23,414 (23.41%)
- Asian: 2,423 (2.42%)
- Black: 10,184 (10.18%)
- Mixed: 2,137 (2.14%)
- Other: 9,051 (9.05%)

Risk of epilepsy higher in Asian infants (RR 2.84, 95% CI [1.57, 5.13], p < 0.001, reference white ethnic group)
Epidemiology of Epilepsy
High income vs low income countries

**Incidence:**
Ngugi et al, *Neurology* 2011;77:1005–1012 (systematic review)

- **High income countries:**
  45/100,000/year
  - (IQR 30.3–66.7)

- **Low + middle income countries:**
  81.7 (IQR 28.0–239.5)

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R Tekle_Haimanot et al, 1997;
H T Rwiza et al, 1992;
K S Mani et al, 1998
North London Epilepsy in Infancy Cohort
Seizure Types (ILAE, 2001)

- Focal (incl secondarily
generalised)
- Generalised
- Focal + generalised
- Undetermined*
- Spasms

18, 32%
27, 46%
9, 16%
2, 4%
1, 2%
Classification of Epilepsies – ILAE
Aetiological Categories

1989/2001 Proposal

• Ideopathic: presumed genetic

• Symptomatic

• Cryptogenic: Presumed symptomatic

2010 Proposal

➢ Genetic

➢ Structural/metabolic

➢ Unknown

http://www.ilae.org/Visitors/Centre/ctf/ctfoverview.cfm
Revised Terminology for Organisation of Epilepsies
Electroclinical Syndromes
ILAE 2010

One example of how syndromes can be organized:
Arranged by typical age at onset

Neonatal period
- Benign neonatal seizures^a
- Benign familial neonatal epilepsy (BFNE)
- Ohtahara syndrome
- Early Myoclonic encephalopathy (EME)

Infancy
- Febrile seizures^a, Febrile seizures plus (FS+)
- Benign infantile epilepsy
- Benign familial infantile epilepsy (BFIE)
- West syndrome
- Dravet syndrome
- Myoclonic epilepsy in infancy (MEI)
- Myoclonic encephalopathy in nonprogressive disorders
- Epilepsy of infancy with migrating focal seizures

Childhood
- Febrile seizures^a, Febrile seizures plus (FS+)
- Early onset childhood occipital epilepsy (Panayiotopoulos syndrome)
- Epilepsy with myoclonic atonic (previously astatic) seizures
- Childhood absence epilepsy (CAE)
- Benign epilepsy with centrotemporal spikes (BECTS)
- Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
- Late onset childhood occipital epilepsy (Gastaut type)
- Epilepsy with myoclonic absences
- Lennox-Gastaut syndrome (LGS)
- Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)^a
- Landau-Kleffner syndrome (LKS)

Adolescence – Adult
- Juvenile absence epilepsy (JAE)
- Juvenile myoclonic epilepsy (JME)
- Epilepsy with generalized tonic-clonic seizures alone
- Autosomal dominant epilepsy with auditory features (ADEAF)
- Other familial temporal lobe epilepsies

Variable age at onset
- Familial focal epilepsy with variable foci (childhood to adult)
- Progressive myoclonus epilepsies (PME)
- Reflex epilepsies

http://www.ilae.org/Visitors/Centre/ctf/ctfoverview.cfm
Electroclinical syndromes – Neonatal Period

Poor outcome
• Early myoclonic epileptic encephalopathy
• Early Infantile epileptic encephalopathy (Ohtahara Syndrome)
  ➢ Onset first 3 months of life
  ➢ Burst suppression pattern on interictal EEG
  ➢ Tonic spams/tonic seizures; myoclonic seizures
  ➢ Aetiologies: developmental cortical malformations, metabolic disorders, genetic conditions (ARX, STXBP1 etc)

Good outcome
• Benign neonatal seizures
• Benign familial Neonatal seizures
  – Aetiology: genetic - KNCQ2, KCNQ3
Electroclinical syndromes – Infancy

Poor outcome

• West Syndrome
• Dravet Syndrome
• Epilepsy of infancy with Migrating Focal Seizures
• Myoclonic encephalopathy in non progressive disorders

Good Outcome (variable)

• Benign Infantile Epilepsy
• Benign Familial Infantile Epilepsy
• Myoclonic Epilepsy in Infancy
  ⇒ (variable cognitive impairment ~ 30%)
• Febrile seizure plus (F+)
How frequently are electroclinical syndromes identified?
# How frequent are electroclinical syndromes?

<table>
<thead>
<tr>
<th>Period</th>
<th>Electroclinical Syndromes</th>
<th>Proportion in childhood epilepsy cohorts</th>
<th>Incidence estimates per live births</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonatal</strong></td>
<td>• Early Myoclonic Encephalopathy (EME) Ohtahara Syndrome (EIEE)</td>
<td>0.2 – 0.5%</td>
<td>0.1/10.000</td>
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<tr>
<td></td>
<td>• Benign familial neonatal seizures (BFNS)</td>
<td>0.2 -1%</td>
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<tr>
<td></td>
<td>• Benign neonatal seizures</td>
<td></td>
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<tr>
<td><strong>Infancy</strong></td>
<td>• West Syndrome</td>
<td>3.7 - 8%</td>
<td>2.9 - 4.7/10.000</td>
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<tr>
<td></td>
<td>• Dravet Syndrome (DS)</td>
<td>1.6 - 2.9%</td>
<td>1:40.900</td>
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<tr>
<td></td>
<td>• Epilepsy of infancy with Migrating Focal Seizures</td>
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<td></td>
<td>• Myoclonic encephalopathy in non progressive disorders</td>
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<tr>
<td></td>
<td>• Benign Infantile Epilepsy</td>
<td>0.5%</td>
<td>0.55/100.000</td>
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<td></td>
<td>• Benign Familial Infantile Epilepsy</td>
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<td></td>
<td>• Myoclonic Epilepsy in Infancy</td>
<td>0.5 – 2.4%</td>
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<td></td>
<td>• Febrile seizures plus (FS+)</td>
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<tr>
<td>Condition</td>
<td>N (%)</td>
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<td>-----------------------------------------------</td>
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<tr>
<td><strong>North London Epilepsy in Infancy cohort (n=57)</strong></td>
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<tr>
<td>West syndrome /Infantile spasms</td>
<td>16 (28%)</td>
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<tr>
<td>(7 structural / metabolic, 1 presumed genetic, 8 unknown cause)</td>
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<tr>
<td>Ohtahara Syndrome</td>
<td>2 (3.5%)</td>
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<tr>
<td>(1 structural / metabolic, 1 unknown cause)</td>
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<tr>
<td>Dravet Syndrome</td>
<td>3 (5.3%)</td>
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<tr>
<td>(2 genetic: SCN1A mutation confirmed)</td>
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<tr>
<td>Benign infantile seizures (non familial)</td>
<td>2 (2.5%)</td>
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<tr>
<td>Myoclonic epilepsy in infancy</td>
<td>1 (1.8%)</td>
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<tr>
<td><strong>Non syndromic epilepsies:</strong></td>
<td>16 (28%)</td>
<td></td>
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</tr>
<tr>
<td>structural / metabolic</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Genetic / presumed genetic</td>
<td>3 (5.3%)</td>
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<tr>
<td>- Epileptic encephalopathy with KCNQ2 mutation</td>
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<tr>
<td>- Monosomy 1p36</td>
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<tr>
<td>- Prader Willi Syndrome (15q11-q13 deletion)</td>
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<tr>
<td>Unknown cause, no syndrome recognised</td>
<td>14 (25%)</td>
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</tbody>
</table>

Eltze et al, 2012
Electroclinical syndromes in childhood epilepsy cohorts
(ILAE 2010)

• Wirrel et al 2011
  – Retrospective (Rochester Epidemiological Project)
  – **Electroclinical syndrome identified:**
    • @ diagnosis 28%
    • @ follow up 29%

  – **Aetiological categories:**
    • Structural / metabolic 28% ( < 1y: 54%)
    • Genetic 22% ( < 1y: 16%)
    • Unknown 50% ( < 1 y: 30%)
North London Infancy Epilepsy Cohort (onset 1-24 months of age)

Aetiologies entire cohort (n=57)

Epileptic Encephalopathies (23/57, 40%)

- Structural/metabolic
- Genetic (3)/presumed genetic (chromosomal abnormalities: 3)
- Unknown
North London epilepsy in Infancy Cohort Aetiologies n=57

Eltze et al; *Epilepsia*. 2013 Mar;54(3):437-45

* Chromosomal abnormalities / Ionchannel-gene mutations
High Yield of relevant MR Imaging abnormalities in Infants < 2 years with newly onset Epilepsy

- 51% - North London Infancy Epilepsy Cohort, (MR review 51 cases 89% of total cohort)
  - Eltze et al, 2012

- 57% - Hospital Based Infancy Seizure Cohort
  - (n=315, MRI data in 57%)
  - Hsieh et al, 2010

- ~ 25% age < 2 years (16% entire cohort) Connecticut Childhood Epilepsy Cohort (MRI data available for 85%)
  - Berg et al, 2010
Outcomes
Recurrent seizures in the first year - outcome -

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Population</td>
<td>Hospital / Clinic 1963-1974</td>
<td>Hospital / Clinic 1971-1976</td>
<td>Hospital / Clinic 1979-1987</td>
<td>Hospital / Clinic</td>
</tr>
<tr>
<td>Design</td>
<td>retrospective</td>
<td>“prospective”</td>
<td>“prospective”</td>
<td>“prospective”</td>
</tr>
<tr>
<td>Follow up</td>
<td>1-24 years (median 3.6y)</td>
<td>5 - &gt;10y</td>
<td>3-&gt;7y</td>
<td>4-10y</td>
</tr>
<tr>
<td>Persisting Epilepsy</td>
<td>56 % (cumulative % after 6 years)</td>
<td>55%</td>
<td>44%</td>
<td>46%</td>
</tr>
<tr>
<td>Normal Development</td>
<td>21%</td>
<td>28%</td>
<td>42% (DQ &gt;= 70)</td>
<td>29%</td>
</tr>
<tr>
<td>Symptomatic cases</td>
<td>60%</td>
<td>44%</td>
<td>43%</td>
<td>66%</td>
</tr>
<tr>
<td>Mortality</td>
<td>12%</td>
<td>4%</td>
<td>11%</td>
<td>10%</td>
</tr>
</tbody>
</table>

* Febrile convulsions and acute symptomatic seizures included.
Connecticut Childhood Epilepsy Cohort (ascertained 1993-1997, age 1 months – 15 years)

- 530 / 61, (63%) actively followed up (median 10.5 years)

- 26.4% Subnormal global cognitive function (IQ < 80)
North London Epilepsy in Infancy Cohort
Results: Bayley III @ Baseline (n=49)

- 27 boys
- age @ epilepsy onset:
  - mean 6.4 m (sd 6.1)
- Composite scores < 80
  - Cognition 63%
  - Motor 63%
  - Language 71%
## Explorative univariate analyses:
*(factorial ANCOVA)*

<table>
<thead>
<tr>
<th>Independent Factor</th>
<th>F - ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epilepsy onset</strong></td>
<td></td>
<td></td>
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<tr>
<td>&lt; 6 months vs &gt; 6 months</td>
<td>F (1,46) = 0.89</td>
<td>0.35</td>
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<tr>
<td><strong>Number of AEDs @ evaluation</strong></td>
<td></td>
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<tr>
<td></td>
<td>F(3,44) = 2.84</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Number of seizures/seizure clusters prior to developmental assessment:</strong></td>
<td></td>
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<tr>
<td>&lt;= 20 vs &gt; 20</td>
<td>F (1,45) = 17.69</td>
<td>0.000</td>
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<tr>
<td><strong>Seizure types:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spasms</td>
<td>F(2,44) = 0.56</td>
<td>0.58</td>
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<tr>
<td>Generalised</td>
<td></td>
<td></td>
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<tr>
<td>Focal and secondarily generalised</td>
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<tr>
<td><strong>Neurological examination:</strong></td>
<td></td>
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<tr>
<td>Abnormal vs normal</td>
<td>F(1,46) = 56.21</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Neuroimaging findings:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>F(2,47) = 5.92</td>
<td>0.005</td>
</tr>
<tr>
<td>Aetiologically uncertain relevance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aetiologically relevant</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EEG – Interictal discharges:</strong></td>
<td></td>
<td></td>
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<tr>
<td>Present vs absent</td>
<td>F(1,44) = 8.51</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Prior Development</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Vineland ADBS composite)</td>
<td>F(1,36)= 22.8</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
North London Epilepsy in Infancy Study
Epilepsy syndrome groups (after initial assessment)
(ILAE 2001)

Follow up cohort n = 32

Lost to follow up n = 17

- 12 moved away or declined participation
- 5 children died (case fatality 9%)
DCF at baseline and follow up

- No difference between DCF baseline and follow up
- after adjustment for:
  - Seizure status (seizure free > 6 month)
  - Aetiologically relevant abnormalities on MRI
  - Abnormal neurology at enrolment
  - Initial EEG normal vs abnormal
  - Number of AED taken when tested at follow up

The developmental outcome 12 months later was determined by the initial developmental function
- Children with newly diagnosed epilepsy < 3 years
- Baseline VABS + annually over 3 years
- N=172 (70% complete data sets):
  - 67% < 2 years at sz onset
  - 29% Epileptic encephalopathy syndrome diagnosis
  - 28% Symptomatic aetiology (majority structural brain abnormalities)
Fig 1. Adaptive behavior scores over time since initial diagnosis of epilepsy in children with none (solid line) versus with 1 or more of the factors associated with poor outcome (dashed line)

Age of onset of epilepsy, pharmacoresistance (PR) and cognitive outcomes

Berg A T et al. Neurology 2012;79:1384-1391

- N=326, epilepsy onset < 8 y, assessed 8-9 y later
- FSIQ not related to age of onset
- PR associated with lower FSIQ
- Significant interaction between age of onset and PR, less impact of PR with increasing age
Age of onset of epilepsy, pharmacoresistance (PR), cognitive outcomes
Berg A T et al. Neurology 2012;79:1384-1391

• Subgroup of children – at baseline assessed with VABS (n=149)
• Lower FSIQ – significant predictors:
  – Initial VABS composite
  – PR
  – Interaction of PR and age
Predictors of intractable epilepsy onset < 3 years

Wirrel et al 2012 (Rochester Epidemiology Project, retrospective 1980-2009)

- 44/127 (35%)
  - median age @ diagnosis 1.1 y (interquartile range 0.4-1.9)
  - Follow up median 6.5y (interquartile range 3.5-14.4 y)

- <= 12 months at diagnosis
  - [OR, 6.76, 95% CI 2.00, 22.84, p = 0.002]

- Developmental delay @ initial diagnosis
  - (OR 20.03, 95% CI 3.49, 114.83, p = 0.0008)

- Abnormal neuroimaging
  - (OR 6.48, 95% CI 1.96, 21.40, p = 0.002)

- Focal slowing on initial EEG
  - (OR 5.33, 95% CI 1.14, 24.88, p = 0.03).
Conclusions:

• In the majority complex epilepsies with cognitive impairment and commonly structural brain abnormalities, higher mortality

• The yield of investigations for underlying aetiologies is high – likely to increase with newer genetic investigation technologies

• Population data on frequency of genetic conditions is lacking

• Consequences for therapeutic interventions
  \(\Rightarrow\) shift from syndrome to aetiology orientated approach
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  – Epilepsy Research UK
  – Foyle Foundation
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@ UCL-Institute of Child Health / Great Ormond Street Hospital

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  - Kristien Verhaert

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  - Helen O’Reilly
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  - S White
  - A Whitney

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  - T Cox