Epilepsy in the developing brain

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Overview

- Neurodevelopmental disorders in children with epilepsy
- Which children are at highest risk of developmental impairments and ultimately intellectual disability/cognitive impairment?
- Determinants of cognitive development
  - Underlying cause
  - Epileptic activity
  - Anti-epileptic therapies
Neurodevelopmental disorders in children with epilepsy

- High rates of learning, intellectual, behavioural and emotional problems
- Community-based studies of all epilepsies in children report:
  - Behavioural problems in 25%
  - Intellectual problems in 20-26%
  - Psychiatric symptoms in 10-30%
  - Autism spectrum disorders in 5%
Primary determinants of development

<table>
<thead>
<tr>
<th>Age at onset</th>
<th>N</th>
<th>Within Normal</th>
<th>Borderline</th>
<th>Mild MR</th>
<th>MR</th>
<th>Devastated</th>
<th>Impaired-NFC&lt;sup&gt;&lt;small&gt;d&lt;/small&gt;&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 years</td>
<td>281</td>
<td>166 (59.1%)</td>
<td>21 (7.5%)</td>
<td>11 (3.9%)</td>
<td>31 (11.0%)</td>
<td>24 (8.5%)</td>
<td>28 (10.0%)</td>
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<tr>
<td>5–9 years</td>
<td>225</td>
<td>192 (85.3%)</td>
<td>8 (3.6%)</td>
<td>6 (2.7%)</td>
<td>10 (4.4%)</td>
<td>2 (0.9%)</td>
<td>7 (3.1%)</td>
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<td>≥10 years</td>
<td>107</td>
<td>93 (86.9%)</td>
<td>2 (1.9%)</td>
<td>4 (3.7%)</td>
<td>4 (3.7%)</td>
<td>3 (2.8%)</td>
<td>1 (0.9%)</td>
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</table>

**Etiology**
- Idiopathic/cryptogenic: 473 (40.6%) (Connecticut), 401 (84.8%) (Connecticut), 25 (5.3%) (Connecticut), 14 (3.0%) (Connecticut), 9 (1.9%) (Connecticut), 3 (0.6%) (Connecticut), 21 (4.5%)
- Symptomatic/secondary: 140 (35.7%) (Connecticut), 6 (4.3%) (Connecticut), 7 (5.0%) (Connecticut), 36 (25.7%) (Connecticut), 26 (18.6%) (Connecticut), 15 (10.7%)

**Syndrome group**
- ILRE: 71 (93.4%) (Connecticut), 3 (4.2%) (Connecticut), 0 (0.0%) (Connecticut), 0 (0.0%) (Connecticut), 1 (1.4%) (Connecticut)
- SFE: 97 (46.4%) (Connecticut), 6 (6.2%) (Connecticut), 5 (5.2%) (Connecticut), 26 (26.8%) (Connecticut), 6 (6.2%) (Connecticut), 9 (9.3%)
- CFSE: 208 (87.0%) (Connecticut), 13 (6.3%) (Connecticut), 9 (4.3%) (Connecticut), 0 (0.0%) (Connecticut), 5 (2.4%)
- IGE: 131 (86.3%) (Connecticut), 6 (4.6%) (Connecticut), 4 (3.1%) (Connecticut), 0 (0.0%) (Connecticut), 8 (6.1%)
- Undetermined: 38 (81.6%) (Connecticut), 1 (2.6%) (Connecticut), 0 (0.0%) (Connecticut), 1 (2.6%) (Connecticut), 1 (2.6%)
- Nonepileptic encephalopathies combined (ILRE-undetermined): 545 (80.2%) (Connecticut), 29 (5.3%) (Connecticut), 18 (3.3%) (Connecticut), 27 (5.0%) (Connecticut), 27 (5.0%)

**Epileptic encephalopathy**
- 68 (20.6%) (Connecticut), 2 (2.9%) (Connecticut), 3 (4.4%) (Connecticut), 18 (26.5%) (Connecticut), 22 (32.4%) (Connecticut), 9 (13.2%)

**Remission status**
- <5 years seizure free: 246 (60.2%) (Connecticut), 15 (4.1%) (Connecticut), 14 (5.7%) (Connecticut), 33 (13.4%) (Connecticut), 19 (7.7%) (Connecticut), 17 (6.9%)
- ≥5 years seizure free: 320 (86.6%) (Connecticut), 15 (4.7%) (Connecticut), 7 (2.2%) (Connecticut), 10 (3.1%) (Connecticut), 1 (0.3%) (Connecticut), 10 (3.1%)
- Followed <5 years<sup><small>c</small></sup>: 47 (26.5%) (Connecticut), 1 (2.1%) (Connecticut), 0 (0.0%) (Connecticut), 2 (4.3%) (Connecticut), 9 (19.2%) (Connecticut), 9 (19.2%)
- AED status:
  - No AEDs: 357 (86.3%) (Connecticut), 17 (4.8%) (Connecticut), 6 (1.7%) (Connecticut), 10 (2.8%) (Connecticut), 2 (0.6%) (Connecticut), 14 (3.9%)
  - Taking >1 AED: 256 (55.9%) (Connecticut), 14 (5.5%) (Connecticut), 15 (5.9%) (Connecticut), 35 (13.7%) (Connecticut), 27 (10.6%) (Connecticut), 22 (8.6%)

- 613 children with new-onset epilepsy followed for median 10 years (Connecticut)
- **Primary determinants of development: early age at seizure onset, underlying cause, frequent seizures and EEG abnormalities, drug-resistance**
  - Berg AT et al. Epilepsia 2008
Early age of epilepsy onset

- More severe conditions
- Brain more vulnerable to insults
- Critical postnatal developmental processes
- Development of skills step-wise, builds on previously acquired skills
Underlying cause

Epileptic activity

Vulnerable substrate

Antiepileptic drugs
Underlying cause: poorer outcomes in ‘symptomatic’ epilepsies
Improving development by treating the underlying cause?

- **Preventable conditions**
  - eg. perinatal hypoglycaemic/HIE injury, post-traumatic epilepsy (public health)

- **Reversible conditions**
  - eg. B6, folinic acid, biotin, creatine, serine deficiency syndromes (supplement), hyperinsulinism (glucose, diazoxide)

- **Treatable conditions**
  - eg. glucose transporter disorder (ketogenic diet), tumours/dysplasias (surgery)

- **Manageable conditions**
  - eg. idiopathic/genetic epilepsies, non-operable focal epilepsies (AEDs, KD, VNS)

- **Irreversible conditions**
  - eg. chromosomopathies, genetic EEs, diffuse brain abn. (AEDs, KD, VNS)

- **Progressive conditions**
  - eg. progressive myoclonic epilepsies, neoplasms, Rasmussen (AEDs)
Frequent seizures and EEG abnormality: epileptic encephalopathy

‘Epileptic encephalopathy embodies the notion that the epileptic activity itself may contribute to severe cognitive and behavioural impairments above and beyond what might be expected from the underlying pathology alone (eg cortical malformation), and that these can worsen over time.’

• Berg et al, Revised ILAE Classification Report, 2010
Epileptic encephalopathy

Underlying cause

Epileptic activity

Cognitive impairment
abilities (motor, language, cognitive etc)

- infant
- preschool
- school-age
- adult

- normal child
- child with static cerebral abnormality (without frequent seizures)
- epileptic encephalopathy
Which children with epilepsy have an epileptic encephalopathy?

- Infants/younger children >> older children and adults
- Particular epileptic syndromes
  - E.g. infantile spasms (West syndrome), Lennox Gastaut syndrome, Landau Kleffner syndrome
- Any epilepsy with
  - very frequent seizures (often multiple daily)
  - prominent epileptiform abnormality on EEG
Infantile spasms

- Most common type of severe epilepsy in infants
- 1:3000 infants
- Many causes

Features of the seizures
- Look like a ‘startle’
- Occur in clusters
- Most commonly on waking
- Multiple times per day

‘Additional features = West syndrome
- Developmental plateau or regression
  - Developmental outcome subnormal in ~80%
  - EEG – ‘hypsarrhythmia’
Effect of treatment lag in infantile spasms (IS) provides evidence of epileptic encephalopathy

- Better developmental outcomes with short lead-time to treatment
  - IS of any cause (except tuberous sclerosis)
    - 16 point IQ drop with 2 month delay to treatment
  - IS due to Trisomy 21
    - Treatment lag <2 months: median IQ 37
    - Treatment lag >2 months: median IQ 14, higher rates of ASD
  - ‘Cryptogenic’ IS (unknown cause AND normal development prior to IS)
    - Treatment lag <1 month: 100% normal cognition
    - Treatment lag 1-6 months: 40% normal cognition

- ‘Dose-dependent’ effect of IS shown in prospective study of tuberous sclerosis
  - Drop in IQ with spasm onset
  - Progressive decline in IQ with increased duration of exposure to IS

- Eisermann, 2003; Kivity, 2004; O’Callaghan, 2011; Humphrey, 2014
Prevention is better than prompt treatment: pre-treatment in tuberous sclerosis

Commencement of preventative vigabatrin improves developmental outcomes at age 2 years
Fewer patients with intellectual disability (14% vs 48%)
Higher mean IQ (92 vs 69)
Screening EEGs +/- vigabatrin pre-treatment is now standard of care in tuberous sclerosis

Jozwiak, 2011
Epilepsy surgery provides evidence that developmental impacts of epileptic encephalopathy are potentially reversible

- Progessive developmental impairment in early-life epilepsies with frequent seizures
- Epilepsy surgery halts developmental decline
- Median 30 point DQ increase with epilepsy surgery before age 1 year

- Berg, 2004; Loddenkemper, 2007
Epileptic encephalopathy: critical points

- Developmental impacts are:
  - Due to the epileptic activity
  - Progressive
  - Potentially reversible

- Developmental impact can be reduced by early diagnosis and early, effective treatment

- Prevention (where possible) is better than early treatment
How does epileptic activity affect development?

- Impede or interrupt normal processes
- Overt brain injury due to excitotoxic neurotransmitter release, local metabolic compromise, inflammation
- Effect on postnatal brain development
  - Cellular excitability
  - Neuronal connections
    - Activity-dependent synaptogenesis
    - Dendritic arborisation
    - Neuronal migration/organisation
  - Neurogenesis
  - Cellular survival
Effects on the neuron

- Cole, 2002

- Ca++ influx
- Early gene activation
- Protein expression
- Kinase activation
- Glial activation
- Neuronal cell loss
- Neurogenesis

Time scale:
- $10^{-3}$ seconds (1 ms)
- $10^{-2}$ seconds (10 ms)
- $10^{-1}$ seconds (100 ms)
- 1 second
- $10^1$ seconds (10 s)
- $10^2$ seconds (100 s)
- $10^3$ seconds (1 min)
- $10^4$ seconds (16.6 min)
- $10^5$ seconds (2.78 hours)
- $10^6$ seconds (4.34 days)
- $10^7$ seconds (58.1 weeks)
- $10^8$ seconds (7.32 years)
- $10^9$ seconds (231.5 years)
- $10^{10}$ seconds (765.4 years)

Seizure

1 min
1 hour
1 day
1 week
Effects on neuronal connections: example of synaptic proliferation and elimination

- Maximum synaptic number/density is between 6-24 months, with subsequent pruning of redundant synapses

- Synaptic elimination and reinforcement is “activity-dependent” and strongly influenced by glutamate/ GABA balance at synapses

- Huttenlocher, 1979
Developmental impacts of antiepileptic drugs (AEDs)

- **Direct evidence:**
  - Phenobarbitone use in infancy for FS prophylaxis was associated with permanent lowering of IQ by 5-10 points.
  - Low IQ, ADHD and autism rates increased in children born to mothers with epilepsy taking AEDs esp. valproate “fetal AED syndrome”

- **Presumed effects:**
  - Effects of AEDs on cognition, fluency, behaviour and mood reported in adults and children presumably relevant in a developmental context.

How do AEDs impact development?

- AED actions different in the immature brain to adults AED due to developmental differences in receptors
  - E.g. GABAergic drugs depolarising
- AED effects can impair cellular and network processes in postnatal brain development
  - Cellular excitability
  - Neuronal connections
    - Activity-dependent synaptogenesis
    - Dendritic arborisation
    - Neuronal migration/organisation
  - Neurogenesis
  - Cellular survival

Reducing impact of AEDs on development

- Consider whether treatment needed at all (may not be in ‘benign’ seizure disorders)
- Understand which AEDs more likely to impact development
  - Phenobarbitone, benzodiazepines, valproate and vigabatrin
- Reduce and rationalise polypharmacy where possible
  - Tailor AED choice to type of epilepsy
  - Optimise drug combinations for efficacy and to reduce pharmacodynamic effects
  - Using non-AED epilepsy treatments to reduce/obviate AED use e.g. epilepsy surgery, vagus nerve stimulator
Underlying cause

Vulnerable substrate

Epileptic activity

Antiepileptic drugs
Recommendations for improving developmental outcomes

- Identify children with epilepsy at risk of impaired development
  - Identify underlying cause (especially treatable causes)
  - Accurately characterise the epilepsy and likely presence of epileptic encephalopathy
    - Guide treatment choice and urgency
  - Rational choice of AEDs (sometimes no AEDs)
  - Get expert advice/assistance in young children with epilepsies that have potential developmental impact
  - Monitor seizure control, EEG, development

- Prevention of epilepsy in high-risk children (e.g. with tuberous sclerosis)
Thank you!