Overview of the epilepsies of childhood and comorbidities

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Epilepsy

• is a common condition – prevalence 0.5%
  • is not a single condition
  • can be difficult to diagnose
  • no single treatment
• misdiagnosis rate is high
• 25% resistant to medication
  • more likely if lesional
• surgical treatment may be an option if localised onset to seizures
Definition of epilepsy

ILAE, Fisher et al Epilepsia 2005, 2014

*a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures.*

**Epilepsy: A disease of the brain**

1. At least two unprovoked (or reflex) seizures occurring more than 24 hours apart;

2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years

3. Diagnosis of an epilepsy syndrome.
Definition of a seizure

A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain

ILAE 2005
Generalised seizures

- Originate at some point within and rapidly engage bilaterally distributed networks
- Can include cortical and subcortical structures but not necessarily the entire cortex
Focal seizures

- Originate within networks limited to one hemisphere
- May be discretely localized or more widely distributed...
Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms.

Degree of awareness usually is not specified.

Due to inadequate information or inability to place in other categories.

Fisher et al Epilepsia in press (ILAE)
Role of investigation

**EEG**: type of epilepsy, unlikely to be diagnostic unless record event
- should be performed on all children presenting with two probable epileptic seizures

**Determining cause**
- **MRI**: performed in all where no clear self limiting syndrome, specifically in children with likely focal onset
- **Genetic evaluation**: particularly children with early onset complex epilepsy
- **Metabolic evaluation**: dependent on clinical presentation eg pyridoxine dependency
1. Seizure types

- Certain that events are epileptic seizures – not referring to distinguishing epileptic versus non-epileptic

- In some settings → classification according to seizure type may be maximum level of diagnosis possible

- In other cases → simply too little information to be able to make a higher level diagnosis
  • eg. when a patient has only had a single event
ILAE 2017 Classification of Seizure Types Basic Version

**Focal Onset**
- Aware
  - Impaired Awareness
- Motor Onset
  - Nonmotor Onset
  - focal to bilateral tonic-clonic

**Generalized Onset**
- Motor
  - Tonic-clonic
  - Other motor
- Nonmotor (Absence)

**Unknown Onset**
- Motor
  - Tonic-clonic
  - Other motor
- Nonmotor
- Unclassified
ILAE 2017 Classification of Seizure Types Expanded Version

**Focal Onset**
- Aware
- Impaired Awareness

**Motor Onset**
- automatisms
- atonic
- clonic
- epileptic spasms
- hyperkinetic
- myoclonic
- tonic

**Nonmotor Onset**
- autonomic
- behavior arrest
- cognitive
- emotional
- sensory

**Generalized Onset**
- Motor
  - tonic-clonic
  - clonic
  - tonic
  - myoclonic
  - myoclonic-tonic-clonic
  - myoclonic-atonic
  - atonic
  - epileptic spasms
- Nonmotor (absence)
  - typical
  - atypical
  - myoclonic
e- eyelid myoclonia

**Unknown Onset**
- Motor
  - tonic-clonic
  - epileptic spasms
- Nonmotor
  - behavior arrest

**Unclassified**
- focal to bilateral tonic-clonic
Etiology
- Tuberous Sclerosis
- GLUT1 deficiency
- Unknown

Seizure types
- Focal onset
- Generalized onset
- Unknown onset

Etiology
- Structural
- Genetic
- Infectious
- Metabolic
- Immune
- Unknown
Structural
• Where unable to make an Epilepsy Syndrome diagnosis or a diagnosis of Etiology

• Many examples
  – Temporal lobe epilepsy
  – Generalized tonic-clonic seizures in a 5 year old with generalized spike-wave
  – Both focal impaired awareness seizures and absence seizures in a patient
  – Cannot tell if tonic-clonic seizure is focal or generalized
‘syndrome’

a group of clinical entities that are reliably identified by a cluster of electroclinical characteristics. Patients whose epilepsy does not fit the criteria for a specific syndrome can be described with respect to a variety of clinically relevant factors
Epilepsy syndromes

- Focal lesional epilepsy
  - Rasmussen Syndrome
- West syndrome
- Lennox Gastaut syndrome
- LKS/ CSWS
- Ohtahara syndrome
- Early myoclonic encephalopathy
- Dravet syndrome
- Epilepsy with myoclonic atonic seizures
- Childhood absence epilepsy
- BECTS
- Migrating focal seizures of infancy
- Panayiotopoulos syndrome
- Juvenile absence
  - Juvenile myoclonic epilepsy
‘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
Dravet syndrome

- 1% of the epilepsy population
- Normal early development/imaging
- Febrile and afebrile general and unilateral prolonged clonic or tonic-clonic s. 1st year of life (100%)
- Later appearance of myoclonus (80%), atypical absences (40%), focal seizures (46%)
- Developmental delay progressively apparent
- Prognosis always unfavorable, for seizures, cognitive development, high mortality rates (up to 15%)
- >80% mutation SCN1A

Effective AEDs
Valproate
Clobazam
Topiramate
Levetiracetam
Ketogenic diet

Newer agents
Stiripentol
Chiron et al Lancet 2000

Seizure aggravation
Carbamazepine, phenytoin
Lamotrigine - Guerrini

Treatments on the horizon
Panayiotopoulos Syndrome

Ictal vomiting may be associated with pallor, pupillary changes, hypersalivation – may become flaccid and unresponsive mimicking syncope

Behavioural change, headache often occur at onset

Confusion, eye deviation, hemi or generalised Szs may develop

= Autonomic epilepsy

EEG may show multifocal or generalised spikes

Occipital spikes predominate - seen in less than 40% in first EEG increasing to 75% in subsequent recordings
Myoclonic Astatic Epilepsy

(Doose syndrome)

• Onset age 18m-60m
• Multiple seizure types
  
  *Myoclonic astatic, absence, tonic-clonic, eventually tonic*

• Initial T/C, increase in frequency
• One third present with stormy course
• Self limited, seizures abate within 3 years 50-89%
• Up to 58% normal cognitive outcome (22% SMR; associated with repetitive NCS)
• VPA, ESM, BNZ, LEV, steroids
Lennox Gastaut Syndrome

Seizure types
- Tonic 74-92%
- Atypical absence 13-100%
- Atonic 14-36%
- Nonconvulsive status 50-75%
- Myoclonus 4-22.5%

EEG
- Diffuse slowing
- Slow- spike wave
- Fast rhythms in sleep

Prognosis
- Medication resistant
  - VPA, LMT, TPM, CLB
- Remission 0-7%
- Characteristic seizures continue
- SSW may be replaced by multifocal independent spike foci

Beaumanoir & Blume 2005
Awake
7y. Impulsive behaviour, learning difficulties

Asleep
Landau-Kleffner syndrome

- Normal early development and language
- Onset before 6 years
- Auditory agnosia
- Cognitive/behaviour/motor problems
- Seizures in 75%, but may be infrequent
- Epileptogenic activity affecting speech cortex
- Posterior temporal foci
Landau-Kleffner syndrome

• Seizures remit by 13-15 years of age in most
• Outcome for language less good:
  10-20% acquire normal language
• Medical treatment- sodium valproate, ethosuximide, clobazam, steroids
• Surgical treatment-multiple subpial transections
Childhood Epilepsy with Centrotemporal Spikes

- Age 5-10 years
- Seizures from sleep
  - Rolandic ‘focal motor’
  - GTC
- Centrotemporal spikes on EEG

*To treat or not to treat?*
Late onset Benign Occipital Epilepsy (Gastaut)

• Age of onset mean 6 years
• Visual seizures
  – Elementary hallucinations, blindness or both
• Hemi (41%) or generalised convulsions (8%)
• Post ictal headache one third
• Treatment carabamazepine
• Full remission in >90% by 19 years
Childhood Absence Epilepsy

- **Onset 4-8 years**
- **Seizure types**
  - Absence seizures
    - Pyknolepsy = frequent
    - Frequent - many / day
  - Generalized Tonic-Clonic Seizures
    - 40%
    - Adolescence
- **Normal intellect**

**EEG**
- Generalized spike-wave activity
- 2.5-3.5 Hz

**Aetiology - Genetic > 1 gene**

**Treatment**
- Sodium Valproate
- Ethosuximide
- Lamotrigine

**Prognosis good**
Juvenile Myoclonic Epilepsy

- Onset 12 - 18 years
- Seizure types
  - Myoclonus
  - GTCS
  - Absences in 30%
- Photosensitive
- Sleep-wake cycle
- Normal intellect
- 4% evolve from CAE

**Aetiology:** Polygenic > 1 gene
  - Rare genes identified
  - Genetic heterogeneity

**Treatment**

- VPA, LVT
- Lifestyle factors are critical - avoid
  - Fatigue
  - Alcohol
  - Photic eg disco strobe lights

**EEG**

- Generalized spike-wave discharges
  - 3.0 - 6.0 Hz
- Polyspike-wave

**Prognosis**

- Good
- Spontaneous remission rare
JME

1 sec

100 µV

F4-C4
F3-C3
C4-A2
C3-A1
A2-T6
A1-T5
T6-Oz
T5-Oz
P4-Oz
P3-Oz
A2-T4
T4-C4
C4-Cz
Cz-C3
C3-T3
T3-A1
*ECG
Goals of management

- Accurate diagnosis
- Prompt and optimal investigation
- Accurate diagnostic & prognostic information for families
- Seizure freedom
- No adverse effects to treatment
- Ease and optimal timing of referral for complex patients
Initial treatment

• **Antiepileptic medication**
  – Similar drugs to adults
  – Data limited in children
  – Guided by epilepsy diagnosis

• **Aim: seizure freedom**
  – Awareness that medication can worsen seizures
When to stop treatment

• Related to epilepsy syndrome

• Benign syndromes;
  • predictability of age

• Evidence for consideration after two years seizure freedom

• Careful consideration
  
  Risk of recurrence - underlying aetiology
  Timing of medication withdrawal
### Psychiatric disorder in epilepsy

**N=10438, age 5-15 years**  
*British Child and Adolescent Mental Health Survey*

<table>
<thead>
<tr>
<th>Group</th>
<th>% with psychiatric disorder (N)</th>
<th>% SLD (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>Emot</td>
</tr>
<tr>
<td>Epilepsy plus (25)</td>
<td>56.0% (14)</td>
<td>16.0% (4)</td>
</tr>
<tr>
<td>Pure epilepsy (42)</td>
<td>26.2% (11)</td>
<td>16.7% (7)</td>
</tr>
<tr>
<td>Diabetes (47)</td>
<td>10.6% (5)</td>
<td>6.4% (3)</td>
</tr>
<tr>
<td>All other (10,202)</td>
<td>9.3% (946)</td>
<td>4.2% (427)</td>
</tr>
</tbody>
</table>

Any, any psychiatric disorder, not including learning disability; Emot, any emotional disorder; Cond, any conduct disorder, including oppositional defiant disorder; ADHD, any attention deficit/hyperactivity disorder; PDD, any pervasive developmental disorder (autistic disorder); SLD, severe learning disability

*Davies S, et al. Dev Med Child Neurol 2003;45:292-5*
Epilepsy and cognition

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

Reversible
New onset epilepsy in infancy


Mean Bayley scores (BS): cognition 84 (55-115, SD=17.67), motor 79.4 (46-124, SD=22.4), language 83 (47-115, SD=17.1).
Neurobehaviour in epilepsy

Cause or consequence?

• Children with new onset ‘idiopathic’ epilepsies assessed prior to AED significant abnormalities
  Oostrom et al 2003

• Academic problems antecedent to onset of epilepsy
  Hermann et al 2006

• Behaviour problems evident at diagnosis, & probably antecedent
  Austin et al 2001

Oostrom et al Pediatrics 2003;112:1338-44
Epilepsy: A disease of the brain

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3. Diagnosis of an epilepsy syndrome.

Epilepsies = a group of diseases
Not all due to epileptiform activity...

• Many disorders not solely due to epileptiform activity
  eg. developmental or behavioural deterioration

• eg. Dravet syndrome- developmental slowing or regression occurs at 1-2 years when epileptiform activity not frequent
  – Suggests both a developmental and epileptic component
  – Both likely secondary to underlying SCN1A mutation

• Where both delayed development and frequent epileptiform abnormalities
  →suggest term “developmental epileptic encephalopathy”

Scheffer et al Epilepsia 2017;58: 512-521
Children with Epilepsy in Sussex Schools (CHESS)

- To characterise the prevalence and spectrum of difficulties in ‘active’ epilepsy (children aged 5-15 years)
  - Cognition (global and specific difficulties)
  - Academic Achievement
  - Behaviour (neurodevelopmental, psychiatric and motor)

- 85 Children (74% of eligible population) underwent assessment.

- DSM-IV-TR consensus clinical diagnoses
CHESS Study – Main Findings

• Cognition/Academic Achievement
  ➢ 24% below IQ 50, 40% below IQ 70 (IDD) 55% below 85.
  ➢ Memory + Processing Speed problems (approximately 50%)
  ➢ 42% displayed academic underachievement

• Behaviour/Psychiatric
  ➢ 60% had DSM-IV behavioural or motor disorder.
  ➢ Only 33% of these had previously been diagnosed.
  ➢ 80% had at least one DSM-IV and/or or cognitive impairment.
  ➢ 34% had IQ below 85 and 1 or more DSM-IV disorder.

Reilly et al Pediatrics. 2014 Jun 1;133(6):e1586-93
Behaviour/Psychiatric/Motor Diagnosis

Reilly et al Pediatrics. 2014 Jun 1;133(6):e1586-93
Sussex Early Epilepsy and Neurobehaviour (SEEN) study

**Recruitment**

- Children with epilepsy born between 2008 and 2014, resident in RH10 to RH14 between 31 August 2014 and 29 February 2016. Had to be at least one year of age at the time of assessment.
- 48 of 53 (91% of eligible children with epilepsy) with epilepsy took part
- A comparison group of 48 gender and age matched children with neurodisability (neurological/neurodevelopmental difficulties)

**Child Assessment**

- Global development, adaptive behaviour, sleep, behaviour.

**Parent Assessment**

- Depression anxiety, stress, sleep and maternal parenting stress
- Interviews with parents of children with epilepsy

*Reilly et al submitted*
Child Development

<table>
<thead>
<tr>
<th></th>
<th>No significant delay</th>
<th>DQ 50-69</th>
<th>DQ&lt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>42%</td>
<td>19%</td>
<td>39%</td>
</tr>
<tr>
<td>Neurodisability</td>
<td>38%</td>
<td>29%</td>
<td>33%</td>
</tr>
</tbody>
</table>
Autism Spectrum Disorder/ADHD

- Had ASD: 17% Had ADHD, 33% Did not Have ADHD
- Did not Have ASD: 60% Had ADHD, 38% Did not have ADHD

- Had ADHD: 29% Had ASD, 17% Did not have ASD
- Did not have ADHD: 31% Had ASD, 38% Did not have ASD
What is Epilepsy?

• Epilepsy should be understood as a Disability Complex (Neville, 1999) - Epileptic Seizures and an increased risk for
  ➢ Cognitive difficulties (Global or Specific)
  ➢ Symptoms of Neurodevelopmental Disorders – ADHD and ASD
  ➢ Symptoms of Emotional Disorders (Anxiety and Depression)
  ➢ A range of motor difficulties including DCD
  ➢ Academic Underachievement

• The additional difficulties frequently constitute the major disability of children with epilepsy

• For many epilepsy is an Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE) disorder
A role for intervention?

• *Early recognition imperative for optimised outcome?*

• Psychology/neurodevelopmental assessment should be available at diagnosis
  – Educational support
  – Mental health intervention
  – Sleep intervention