Childhood Epilepsy - Overview & Update

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NO DISCLOSURES
Videos
Outline: Childhood Epilepsy

- What is it?
- How do we classify it?
- How do we diagnose it?
- How do we treat it?
- Emerging treatments
- Precision medicine
- Service in Ireland

Definitions

The Epilepsies

A large group of conditions that cause recurrent epileptic seizures

- The Epilepsies occur in the setting of hundreds of neurological conditions
- Some benign and some more devastating
- Physical, Social, cognitive

Also 1 seizure if risk of subsequent seizures is high

- COL4A2 mutation
  - 1 seizure but status epilepticus x 30 min
How common is Epilepsy?

**Prevalence:** 0.5% children (5/1000)

Other Facts

- 100,000 children and adolescents each year
- 50% patients feel stigmatised
- Four-fold risk of co-morbidities with reduced QOL
Seizure

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

Seizures are a manifestation of the Epilepsy
Clinical or Electrographic

VIDEO

Presentation of Epilepsy

Focal seizure ("partial")
~65%
Aware or LOC
Structural
Genetic

Generalised seizure
~25%
Loss of Consciousness
Toxic
Atonic
Myoclonic
Absence
Genetic

Infantile Spasms
~5%
Structural
Genetic

Wirrel, 2011; Blume et al, Epilepsia 2001; Berg et al, 2010
2 videos focal tonic with secondary generalisation

Infantile spasms

Lots of things can look like epilepsy

Up to 30% paediatric tertiary referrals not epilepsy!

- Collapse/Loss of Consciousness
- Confusional attack/amnesia episode/staring/altered awareness
- Movement Disorder
- Sleep Disorder
- Epileptic or Non-epileptic presentations

- Age-dependent
  - Neurologically normal or abnormal
  - Diagnose or Exclude Epilepsy (worthy differential)

Over-diagnosis of Epilepsy = Inappropriate tests (EEG, treatment/stigma/restrictions)
Diagnosis of Epilepsy?

- **History and observation**
  - Understand the seizure types
  - Understand the mimics
  - Understand the tests

- **Electroencephalogram (EEG)**
  - Support diagnosis
  - Yield: 60%
  - Yield: Serial EEG x 3 = 90%
  - Yield: Sleep

**EEG / Electro-encephalogram**

False positives 5%

**Misuse of EEG testing – not for:**

- “funny turns” when clear history e.g. fainting, reflex anoxic syncope
- Day-dreaming / deterioration in behavior in autism
- Typical febrile seizures
- Drug withdrawal (established benign focal)
- Established epilepsy when substantial structural abnormalities - clinical change in seizure
- Pronged hallucinations in psychiatric patients

NICE 2012; 2004; MOC, Ireland
Causes of Epilepsy

- Genetic
  - Mitochondrial etc
  - GLUT1-deficiency
  - Vitamin-dependent
  - Monoamine metabolite
- Structural
- Metabolic

MRI Scan
- Under 2 years
- Focal epilepsy
Causes: Genetic (in our DNA)

Genes code for proteins that function to control nerve signalling and transmission
Human DNA Sequence (Genome)

Read in book ~ 30 years

Finding the culprit gene has been difficult unless you know what you are looking for

Many genes ~20,000

Since 2009: Genome sequencing

Patient’s DNA can be amplified and sequenced on a computer

Based on Clinical Objective & Chosen Platform → Gene discovery - Many genes
Genes & Epilepsy

- Genome Sequencing or Gene panel test

**Sample Epilepsy Gene Panel**

<table>
<thead>
<tr>
<th>Gene</th>
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<td>PROTHE1</td>
<td>SLC35A2</td>
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Epilepsy: Causes

**Genetic TESTING**

- **SEVERE EARLY ONSET EPILEPSY**
  - Copy Number Variants / Chromosomal array 5-10%
    - Refractory epilepsy
    - Eg. 15q, T21, Ring 20
  - Single genes/Panels
    - Now ~ 50% in epileptic encephalopathies
    - Familial (e.g. focal epilepsies)
    - Genes for some “structural” causes e.g. dysplasias

- **LESS SEVERE / MORE COMMON EPILEPSIES (E.G. IGE/IFE)**
  - Complex Genetic
    - Multiple combined variants/genes, subtle regularity
Severe Early Onset Epilepsy - Value Patient, Family, Clinician

- Understand cause molecular level

- Genetic Counselling
  - Help predict natural history and prognosis

- Reduced visits, Reduce testing (invasive etc), Reduce Cost

- Reduce Anxiety

- Treatments

- Supports

Research Perspectives: Genomics

Ireland?

Plans in Near Future

Link Data with International Groups

http://www.cureepilepsy.org/egi/index.html
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Epilepsy Treatment

Prevent & Abolish Seizures
Maximise QOL

- Treat Seizure
- Treat Epilepsy syndrome
- Treat cause

Minimise side-effects
- AEDs
- MDT involvement
- Access to services
Drugs - Seizure-based approach

Focal seizure
- Osacebamazine
- Levetiracetam
- Lamotrigine
- Topiramate
- Valproate
- Vigabatrin
- Phenytoin
- Phenobarbitone
- Benzodiazepines
- Gabapentin

Generalised seizure
- Tonic
- Clonic
- Tonic
- Atonic
- Myoclonic
- Absence

Infantile Spasms
- Prednisolone
- Vigabatrin
- Clonazepam

- Lamotrigine
- Levetiracetam
- Topiramate
- Benzodiazepines

Tonic
- Clonazepam
- Levetiracetam
- Topirimate
- Benzodiazepines

Absence
- Ethosuximide

Modified from Pellock

Treatment of Electro-clinical pattern

- Seizure types
- EEG
- Age of onset

Electro-clinical pattern

1/3rd of EPILEPSIES

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

- Infantile
  - Focal seizures
  - Hemispheric focal seizures
  - Benign familial neonatal epilepsy (BFNE)
  - Ohtahara syndrome
  - Early Myoclonic Encephalopathy (EME)
  - Myoclonic encephalopathy in non-epileptic disorders
  - Epilepsy of infancy with migrating focal seizures

- Childhood
  - Focal seizures: infantile spasms
  - Febrile seizures plus
  - Early onset childhood absence epilepsy
  - Lennox-Gastaut syndrome
  - Lennox-Gastaut syndrome (LGS)
  - Late onset childhood absence epilepsy
  - Lennox-Gastaut syndrome (LGS)
  - Epilepsy with myoclonic absence
  - Lennox-Gastaut syndrome (LGS)
  - Early onset childhood absence epilepsy
  - Early onset childhood absence epilepsy
  - Autoimmune absence epilepsy with auditory features (AASE)
  - Other benign focal epilepsy

- Adolescent
  - Infantile spasms
  - Febrile seizures: infantile spasms
  - Infantile spasms: infantile spasms
  - Infantile spasms: infantile spasms
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  - Infantile spasms: infantile spasms

ILAE

8/03/2016

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AEDs by Electro-clinical Syndrome (e.g. NICE guidelines)

<table>
<thead>
<tr>
<th>Childhood absence epilepsy (other absence syndromes e.g. JAE)</th>
<th>First-line AEDs</th>
<th>Adjunctive AEDs</th>
<th>Consider</th>
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<tbody>
<tr>
<td>Ethosuximide*</td>
<td>Ethosuximide*</td>
<td>Lamotrigine*</td>
<td>Sodium valproate</td>
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<tr>
<td>Lamotrigine*</td>
<td>Lamotrigine*</td>
<td>Valproate</td>
<td>Topiramate*</td>
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<tr>
<td>Valproate</td>
<td>Topiramate*</td>
<td>Topiramate*</td>
<td>Sodium valproate</td>
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<table>
<thead>
<tr>
<th>Juvenile myoclonic epilepsy</th>
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<tr>
<td>Levetiracetam*</td>
<td>Lamotrigine*</td>
<td>Levetiracetam*</td>
<td>Topiramate*</td>
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<td>Valproate</td>
<td>Topiramate*</td>
<td>Sodium valproate</td>
<td>Topiramate*</td>
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<thead>
<tr>
<th>Benign Rolandic &amp; Panayiotopoulos syndrome</th>
<th>Carbamazepine*</th>
<th>Levetiracetam*</th>
<th>Sodium valproate</th>
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<tbody>
<tr>
<td>Lamotrigine*</td>
<td>Carbamazepine*</td>
<td>Levetiracetam*</td>
<td>Topiramate*</td>
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<tr>
<td>Ethosuximide*</td>
<td>Levetiracetam*</td>
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<td>Sodium valproate</td>
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**EPILEPTIC ENCEPHALOPATHIES**

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<thead>
<tr>
<th>First-line AEDs</th>
<th>Consider</th>
<th>Avoid</th>
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<tbody>
<tr>
<td>Infantile spasms (or ACTH)</td>
<td>Vigabatrin</td>
<td>Carbamazepine, gabapentin, lamotrigine, eslicarbazepine, phenytoin, pregalbamine, tiababoline, vigabatrin</td>
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<table>
<thead>
<tr>
<th>Dravet syndrome</th>
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<td>Valproate</td>
<td>Topiramate*</td>
<td>Stripentol</td>
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<tr>
<td>Valproate</td>
<td>Lamotrigine</td>
<td>Ketogenic diet</td>
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<tr>
<td>Valproate</td>
<td>Levetiracetam</td>
<td>Ketogenic diet, VNS</td>
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<tr>
<td>Valproate</td>
<td>Carbamazepine, levetiracetam, clobazam, stiripentol, valproate, ethosuximide, ketogenic diet, VNS</td>
<td>Benzo small risk triggering tonic status, same if myoclonic seizures regarding risk</td>
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</tbody>
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<thead>
<tr>
<th>Lennox–Gastaut syndrome</th>
<th>Valproate</th>
<th>Carbamazepine, lamotrigine, ketogenic diet</th>
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<tr>
<td>Valproate</td>
<td>Lamotrigine</td>
<td>Clobazam*</td>
</tr>
<tr>
<td>Valproate</td>
<td>Levetiracetam</td>
<td>Carbamazepine, levetiracetam, clobazam, ketogenic diet</td>
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<tr>
<td>Valproate</td>
<td>Carbamazepine, clobazam, levetiracetam, ketogenic diet</td>
<td>Carbamazepine, phenytoin, vigabatrin</td>
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<tr>
<th>Myoclonic-astatic epilepsy</th>
<th>Valproate, levetiracetam, ketogenic diet</th>
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<tr>
<td>Valproate</td>
<td>Lamotrigine*</td>
</tr>
<tr>
<td>Valproate</td>
<td>Stiripentol</td>
</tr>
<tr>
<td>Valproate</td>
<td>Carbamazepine, levetiracetam, ketogenic diet</td>
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<th>Continuous spike and wave during slow sleep / ISES</th>
<th>Valproate, stiripentol, ethosuximide, ketogenic diet</th>
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<tbody>
<tr>
<td>Corticosteroids, clobazam</td>
<td>Valproate, levetiracetam, ethosuximide, ketogenic diet</td>
</tr>
</tbody>
</table>

Newer Generation Antiepileptic Drugs

**Place uncertain: less experience with longer term follow up and efficacy**
Newer AEDs: children

• Observations
  – Lacosamide: refractory focal epilepsy
  – Perampanel: refractory generalised and focal
  – Brivaracetam: ?
  – Eslicarbazepine:?
  – Cannabidiol:
    • Refractory patients with LGS, epileptic encephalopathies where other drugs have failed
    • Trials ongoing
  – Everolimus: Tuberous Sclerosis
    • Clinical significant difference in significant number of patients
    • Trials ongoing

SEIZURE PROGNOSIS

• 50-60% Childhood Epilepsies Remit
  – Benign focal epilepsies (20-30%): few years / treatment can be avoided
  – Pharmaco-sensitive group e.g. CAE (30%): control easy /Spontaneous remission years

• Pharmaco-dependent 20%
  – Control but no spontaneous remission/relapse/lifelong e.g. JME/subset of IFEs

• Pharmaco-resistant (medically refractory) 20%
  – Epileptic encephalopathies and subset of structural focal epilepsies
  – Further treatment
Medical Refractory Epilepsy

Other Therapies

• Neurosurgery

• Ketogenic Diet

• Stimulators

• Alternative

Epilepsy Surgery

• 60-70% cure rate if suitable
**Ketogenic Diet**

- >50% patients seizure reduction
- Small % seizure free

**Neuro-Stimulation**

Vagus Nerve Stimulation
- 1/3rd > 50% reduction
- 1/3rd < 50% reduction
- Reduced anti-seizure drugs
- Non seizure outcome: mood, alertness, QOL, memory
- Magnet
Medically refractory Patients.
Current treatment anti-epileptic drugs
Hardly Precision Medicine!

The scientific basis that underpins the personalisation of medical care, particularly in the context of treatments targeted towards the precise molecular (genetic) causes of disease.
Genetic Landscape: Severe Epilepsies

New Mechanisms, New Pathways, New Drugs

<table>
<thead>
<tr>
<th>Patient</th>
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<tbody>
<tr>
<td>Phenotype</td>
<td>Genotype</td>
<td>Genetics</td>
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<tr>
<td>Migrating partial seizures of infancy</td>
<td>SCN1A</td>
<td>GRIN2A</td>
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<td>Dravet syndrome</td>
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<tr>
<td>Multifocal epilepsy (ESES)</td>
<td>TSC1/TSC2</td>
<td>TSC1/TSC2</td>
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Quinidine (Bearden et al, 2014)
Clemizole (Piereson, 2014)
Memantine (Piereson, 2014)
Everolimus

Also Gene Therapies

From: Allen, King, Delanty, McTague

Epilepsy Treatment

Abolish Seizures
Rescue medication
Maximise QOL
Epilepsy Review Clinic for Dummies

- Epilepsy
  - Type, Cause, Duration
- Current Medications
  - Doses (mg/kg/day)
  - Recent level if relevant
- Past Medications
- EEG
  - Initial, last and recent (evolution)
- MRI results
- Seizure update
  - Types
- Development
  - School/Academic/social progress etc.
  - Associations
- Investigations etc if not known why patient has epilepsy

*Rescue medication*
- Formulation & Plan: Clearly written

Buccal Midazolam: Emergency (rescue)

Indications (community)
- Prolonged generalised tonic clonic seizure (GTCS) > 5 min
- Tonic seizures with cyanosis or prolonged > 5 min
- If seizures cluster over short period (day) with progression to prolonged GTCS
- Live in remote area with a prolonged ambulance response time: Known GTCS
- If required frequently in the past and weaning off AED (give x2y)

2nd Dose
- If 1st not effective within 15-20 mins (provided continuing to escalate/spread)
- Justified if used before (e.g. twice <24 h) and no respiratory depression

NOT indicated
- Prolonged CPS with a minimal motor or respiratory component
- Occipital lobe seizures with no effect on breathing or cyanosis
- Requests for other reasons ☻
Use of Technology

• Smart Phones
  – Record seizures
  – Phone app (diary, medications etc)

• Seizure detection systems (give intervention)
  – Movement sensors, accelerometers, physiological devices, EMG, video + infrared, dogs
  – Careful & individual consideration
    • Lack of large scale studies comparing them
    • False positives etc
    • However likely will improve (INTEGRATED DEVICES)

• Electronic Patient Records

Epilepsy Treatment

Abolish Seizures
Rescue medication

Maximise QOL

Remove Stigma
MDT involvement
Access to services
Improving Access to Services

• Model of Care for Children
• Paediatric Neurology / Epilepsy Service
• Managed clinical network
  – Enhanced communication
    • Specialist clinics regional
    • Integrated
      – Care pathways
      – Data management
• Service
  • Close to home as possible
  • Based on expertise & resources

Summary

• Epilepsy = The Epilepsies = group conditions affecting brain = seizures
• Most respond to drugs (many drugs/ newer versus older)
• Intellectual disability or autism broadly treat same principles
• Medically refractory 20-30%
  – Other treatments
• Genomics Explosion
  – Diagnosis increasing
  – Difficult epilepsies - Value to family & patient:
  – Novel gene discovery - understanding (micro level) – similar for autism
  – Specific therapy
• Goal to abolish seizures and improve quality of life
  – Recognise & treating co-morbidities e.g. autism, ADHD (>10% have epilepsy)
“There is no subject so old that something new cannot be said about it”

Fyodor Dostoyevsky (1821-1881)