Epilepsy in children

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What's new?

• Exciting options in terms of diagnostics – neurophysiology and genetics - as well as surgical techniques

• Basic principles remain unchanged

• Clinician needs to decide whether an event is an epileptic seizure – and as always relies on HISTORY and examination. Video recordings have become invaluable – “that’s it” EEG open to abuse!

• The diagnosis of epilepsy remains clinical and requires “at least two unprovoked seizures”

• Misdiagnosis of epilepsy 20 – 30%
“..faints and funny turns..”

• Many many mimics – some easy to recognize, some more tricky
• Some examples:
  1. *Syncope and Anoxic Seizures*: Vasovagal syncope, Reflex anoxic seizures, Breath holding Spells, Long QT syndrome and cardiac syncope
  2. *Behavioural, Psychological*: Daydreaming / inattention, Infantile gratification, Tantrums and rage reactions
  3. *Sleep related*: Parasomnias, Narcolepsy-cataplexy, Benign neonatal sleep myoclonus
  4. *Paroxysmal Movement Disorders*: Tics, Stereotypies, Paroxysmal dyskinesias, Hyperekplexia
  5. *Migraine*
  6. *Other*: Jitteriness, Shuddering attacks
Red flags - cardiac syncope

• Syncope during exercise or sleep
• Family history of sudden death in person < 30 years of age
• Investigation recommended for “first seizure” by BPNA: ECG
• Calculate QTc interval / use normogram
• Normal <0.44 seconds
New ILAE classification - 2017

Scheffer et al
Epilepsia 2017
2017 ILAE Epilepsy Nomenclature

Level 1
- Seizure types
  - Focal
  - Generalized
  - Unknown

Level 2
- Epilepsy types
  - Focal
  - Generalized
  - Combined Generalized & Focal
  - Unknown

Level 3
- Epilepsy syndromes

Focal Onset
- Classified to either:
  - Aware
  - Impaired awareness
- Motor Onset
- Non-motor Onset
  - May progress to:
    - Focal to bilateral tonic-clonic

Generalised Onset
- Classified to either
  - Motor
    - Tonic clonic
    - Other motor
  - Non-motor
    (Absence seizures)

Unknown Onset
- Classified to either
  - Motor
    - Tonic clonic
    - Other motor
  - Non-motor
  - Unclassified

Aware = Awareness during the seizure, knowledge of self and environment, consciousness is intact.
Motor = Movement or motion
Unclassified = Seizures with patterns that do not fit into the other categories or there is insufficient information to classify the seizure
ILAE 2017 Classification of Seizure Types Expanded Version

Focal Onset

- Aware
- Impaired Awareness

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

- Non-Motor Onset
  - autonomic
  - behavior arrest
  - cognitive
  - emotional
  - sensory

  focal to bilateral tonic-clonic

Generalized Onset

- Motor
  - tonic-clonic
  - clonic
  - tonic
  - myoclonic
  - myoclonic-tonic-clonic
  - myoclonic-atonic
  - atonic
  - epileptic spasms

- Non-Motor (absence)
  - typical
  - atypical
  - myoclonic
  - eyelid myoclonia

Unknown Onset

- Motor
  - tonic-clonic
  - epileptic spasms

- Non-Motor
  - behavior arrest

Unclassified

1 Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms

2 Degree of awareness usually is not specified

3 Due to inadequate information or inability to place in other categories
Aetiology

- Structural
- Genetic
- Infectious
- Metabolic
- Immune
- Unknown
Structural SEGA

Genetic Tuberous Sclerosis
Aetiology

- Think about aetiology at each level
- Impact on treatment and prognosis
- Genetics is a rapidly expanding field - though in most cases the underlying genetic defect is not yet known
  - “Channelopathies” e.g. potassium channel genes (KCNQ3) autosomal dominant Benign Familial Neonatal Epilepsy; Sodium channel SCN1A in Dravet Syndrome and GEFS+ (severe and mild phenotypes from the same mutation)
- Genetic does NOT mean inherited – de novo mutations
- Single genes / copy number variants / multiple genes +/- environmental contributions
- Also susceptibility variants contributing to epilepsy but not causative on its own
Epilepsy types

May be the final “level” – unable to make a diagnosis of Epilepsy Syndrome

• EEG data incorporated
• Focal epilepsy: temporal epilepsy due to mesial temporal sclerosis
• Generalized epilepsy with spike wave activity on EEG
• Think aetiology at every step of the way
Epilepsy syndromes

- Seizure type + EEG - “electroclinical syndromes”
- Age dependent – age of onset and remission
- Treatment and prognostic implications

<table>
<thead>
<tr>
<th>Neonatal / Infancy</th>
<th>Childhood</th>
<th>Teenage</th>
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<tbody>
<tr>
<td>• Benign Familial Neonatal Epilepsy</td>
<td>• Childhood Absence</td>
<td>• Juvenile Abscence</td>
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<tr>
<td></td>
<td>• Childhood epilepsy</td>
<td>• Juvenile Myoclonic Epilepsy</td>
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<td></td>
<td>with centro-temporal spikes</td>
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<tr>
<td>Idiopathic Generalized Epilepsies</td>
<td>Self-limited focal epilepsies</td>
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<td>------------------------------------------------</td>
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<tr>
<td>• Childhood Absence Epilepsy</td>
<td>• Self limited epilepsy with centrotemporal spikes (Rolandic)</td>
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<tr>
<td>• Juvenile Absence Epilepsy</td>
<td>• Self limited occipital epilepsies of childhood</td>
<td></td>
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<tr>
<td>• Juvenile Myoclonic Epilepsy</td>
<td>• Panayiotopoulouos</td>
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<tr>
<td>• Generalized tonic clonic seizures alone</td>
<td>• Late onset form - Gastaut</td>
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Treatment

• Knowing the diagnosis guides treatment and gives more certainty when talking about prognosis

• **Childhood Absence Epilepsy:**
  • First line drugs: Ethosuximide and Sodium Valproate equally effective
  • Second line drug: Lamotrigine
  • Carbamazepine inappropriate
  • Outlook for remission favourable
• Majority of childhood epilepsies respond favourably to treatment with anti-epileptic drugs (70 – 80%) - “Pharmacoresponsive”
• In some very good chance of remission / “to outgrow” – e.g.
  • CAE
  • “Benign Rolandic Epilepsy” – self-limited epilepsy with centrotemporal spikes
  • Self-limited occipital epilepsies of childhood
• Delay in starting treatment no effect on eventual outcome

However...
Epileptic Encephalopathies

• THESE ARE DIFFERENT

• “THE EPILEPTIC ACTIVITY ITSELF MAY CONTRIBUTE TO SEVERE COGNITIVE AND BEHAVIOURAL IMPAIRMENTS” – both ictal AND interictal activity!

• Previously known as “Catastrophic Epilepsies”

• Age dependent disorders – typical EEG patterns, loss of neurological function over time, seizures

• This is the one place where you “treat the EEG” – aim is to normalize the EEG IN ADDITION TO seizure control

• The ultimate aim is to modify the disease

• TIME IS OF THE ESSENCE – need for EARLY treatment
<table>
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<tr>
<th>Epileptic encephalopathies</th>
<th>Most childhood epilepsies</th>
</tr>
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<tbody>
<tr>
<td>• Treatment aimed to modify disease</td>
<td>• Treatment to prevent seizures</td>
</tr>
<tr>
<td>• Early treatment needed – improved outcome</td>
<td>• Delay in starting treatment does not alter longterm prognosis</td>
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<tr>
<td>• Role of immunotherapies</td>
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Epileptic Encephalopathies: Age dependent

Neonatal
- Ohtahara syndrome
- EME (Early Myoclonic Epilepsy)

Infancy
- West syndrome
- Dravet syndrome

Childhood
- Lennox Gastaut Syndrome
- ESES (Electrical Status Epilepticus in Sleep) / CSWS
West syndrome - prototype

- Infantile spasms
  3-8 months old baby

- EEG - Hypsarrythmia

- Devastating Developmental regression / arrest

West syndrome
<table>
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<tr>
<th>Aetiology</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>• Structural (most) – brain malformations, Tuberous Sclerosis, HIE / Genetic / Unknown</td>
<td>• Hormonal Rx clearly superior ACTH first line; unclear if oral steroids same efficacy into EEG normalisation. High dose 8 mg/kg/d (20-40 mg) prednisone better results (but non-randomized)</td>
</tr>
<tr>
<td>• Outcome depends on aetiology and time taken till EEG normalized and spasms controlled</td>
<td>• ? Whether oral prednisone is to be considered first line</td>
</tr>
<tr>
<td>• Unknown aetiology group when diagnosed and treated early may have normal development</td>
<td>• Vigabatrin first choice in TS</td>
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<td>• Combination Vigabatrin with hormonal therapy may be better – early results from ICISS</td>
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Treatment of epilepsy

- Drugs
- Diet
- Neuromodulation
- Surgery
Anti Epileptic Drugs (AED)
**Intractable epilepsy**

- Despite increasing number of drugs becoming available, percentage of epilepsies unable to control with medication remains at 30%
- By the time the third drug needs to be added, dealing with an intractable epilepsy and you are in trouble!
- Options:
  - Keep trying alternative drugs
  - Alternative treatment modalities
  - Knowledge of aetiology of UTMOST importance
A word about Cannabis

• Used in 1800’s as an AED
• Contains more than 80 different active cannabinoids. THC = main psychoactive component; CBD = main active component in medical use
• NMDA receptor antagonist
• Lots of anecdotal evidence, lots of hype
• Available in SA at health stores, pharmacies like Dischem and over the internet – can buy for yourself and your pet!
• Can be used for “therapeutic purposes” - 0% THC
• Multicentre study – 1st prospectively collected data of cannabidiol use in patients with epilepsy

• Estimates of safety, tolerability, and efficacy in children and young adults with treatment-resistant epilepsy

• “cannabidiol might be an effective treatment option for children and young adults with intractable epilepsy. Randomised controlled trials are warranted to characterise the safety profile and true efficacy of this compound” ,“..potential role for cannabinoids of relevance to epilepsy”

• “there are as yet , no good studies to support their widespread use…..Cannabinoids should be avoided by those with epilepsy, especially the young, who are already at risk of psychiatric problems, until good clinical trials support their use”
Diet

• Ketogenic diet: Proven efficacy in GLUT – 1 deficiency and Dravet
• Worth a try in intractable epilepsy
• Breakfast 15 kg: 70ml cream, ¼ apple, ½ egg, 3 teaspoons butter…..
• Alternative approach: Atkins diet
Surgery for Epilepsy??

• Yes!! CONSIDER IN INTRACTABLE (focal) EPILEPSY
• 2% of epilepsy patients successfully treated
• Best case: focal epilepsy + lesion + EEG
• “Lesional” cases: 70% chance of becoming seizure free vs 34% extratemporal non lesional epilepsy
• Mesial Temporal Sclerosis: up to 80 % seizure free 2-5 years after surgery
• Morbidity: 3% major and 7% minor complications
• Mortality: 0.1 – 0.5% = to annual rate of SUDEP in refractory epilepsy
• Cost effective treatment: start saving after 4 years in adults and after 1 year in children
• New developments: non invasive imaging, stereotactic EEG
• New developments on horizon in terms of minimal invasive surgery: e.g. stereotactic laser ablation / thermo-coagulation, highly focused ultrasound, robotics...
Despite improved outcomes, low mortality and new techniques, remains underutilized in high income countries with number of cases remaining stable and referrals in Europe said to be decreasing. Good candidates are not referred to tertiary epilepsy centre (>60% in Dutch study) where available or after a long time lag – 13 – 18 years even!

- In low income countries performed in less than 20% of suitable patients
- ILAE 2003: “disabling seizures failing first line drugs should be referred to an epilepsy centre”
- What is lost can not be regained; function at baseline important determinant of outcome
Neurostimulation

• Option in intractable epilepsy not suitable for surgery
  • Non lesional
  • Epileptic focus in non-resectable area (“eloquent cortex”)
• Considered as palliation but extended seizure free periods in some patients

Options:
• Vagal Nerve Stimulation (VNS)
• Deep Brain Stimulation (DBS)
• “Responsive neurostimulation” – (not approved) – placement of electrodes in epileptogenic zone
Vagal Nerve Stimulation

• Improvement over years
• Next generation devices: detection of increased heart rate – able to deliver bigger impulse in response. May have a protective role in SUDEP
Deep Brain Stimulation

- Placement in Thalamus or Hippocampus
- Reduction of seizures in 40% improving to 69% in 5 years
- Significant improvement in quality of life scores, attention, mood
- 34% adverse events..
Epilepsy has a significant impact on quality of life beyond the seizures. It includes learning problems, underachievement at school, emotional problems (depression) and social status achieved. It also involves exclusion and decreased participation.
Co-morbidities Childhood Epilepsies

• British Mental Health Survey (1999) – high rate of comorbidities in children with epilepsy as per parental questionnaire

• Compared to group of more than 10 000 children, 37% of the children with epilepsy had some comorbidity vs 9% control

• Emotional comorbidity: 16% vs 4%
• Conduct disorder: 19% vs 5%
• Autism Spectrum Disorder: 6% vs 0.2%
Structured interview at 23 years - 56 patients who had Absence Epilepsy (CAE and JAE) and 61 patients with Juvenile Rheumatoid Arthritis

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<thead>
<tr>
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<th>Absence Epilepsy</th>
<th>JRA</th>
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<tbody>
<tr>
<td>Symptoms in last year</td>
<td>34%</td>
<td>72%</td>
</tr>
<tr>
<td>Behaviour problems</td>
<td>41%</td>
<td>10%</td>
</tr>
<tr>
<td>Unplanned pregnancy</td>
<td>34%</td>
<td>3%</td>
</tr>
<tr>
<td>Psychiatric / Emotional</td>
<td>54%</td>
<td>31%</td>
</tr>
<tr>
<td>Unskilled labourer</td>
<td>53%</td>
<td>16%</td>
</tr>
<tr>
<td>Upper level manager / professional</td>
<td>0%</td>
<td>29%</td>
</tr>
<tr>
<td>Not working in area trained</td>
<td>50%</td>
<td>14%</td>
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Conclusion

• Description of seizure type according to ONSET (first prominent symptom)
• Aetiology – impact on treatment. In particular exclude structural lesion in focal epilepsy and consider referral for surgical evaluation
• Recognize the Epileptic Encephalopathies – start treatment as early as possible
• For the majority of childhood epilepsies: prognosis good either for remission or pharmacoresponsiveness
• Be aware of the impact of diagnosis on other areas of a child’s life