Epileptic Seizures and Non Epileptic Events in Children

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Objectives

- Definitions
- Neurobiology of epileptic seizures
- Epidemiology of seizures and epilepsy
- Classification of seizures
- Video examples of seizures
- Differential diagnosis of seizures in childhood
- Epilepsy syndromes in childhood
Definitions

• An epileptic seizure is a transient occurrence of signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.

• Epilepsy is a group of disorders characterised by recurrent unprovoked epileptic seizures

• Epileptic syndromes refer to disorders with characteristic seizure types and EEG abnormalities

• Sometimes these syndromes are also associated with common aetiologies and prognosis.
Neurobiology of Epilepsy

- Neurones are polarised cells with a soma, axon and dendrites

- Axons transmit action potentials in all or none fashion

- Dendrites receive information from neurones via synapses

- Synaptic transmission occurs via release of neurotransmitters from the presynaptic nerve terminal

- Neurotransmitters combine with receptors resulting in ion flow through “Ligand Gated” channels
Glutamatergic Excitatory Neurotransmission

Glutamate allows entry of positively charged ions into the cell resulting in neuronal depolarisation
Action Potential

0mV

Resting Membrane Potential
-70mV

Depolarisation

Repolarisation

Overshoot

Hyperpolarisation
GABAergic Inhibitory Neurotransmission

GABA allows entry of negatively charged ions into the cell resulting in neuronal hyperpolarisation.
Neurobiology of Epilepsy

• Two classes of neurones
  – Excitatory neurones that release glutamate, generate EPSPs
  – Inhibitory neurones that release GABA, generate IPSPs

• Epileptic seizures result from either an excess of excitation or lack of inhibition

• “Hyperexcitability and hypersynchronisation”
Epidemiology of Seizures and Epilepsy

- 3-5% of people will have one or more seizures in their lifetime
- Prevalence of epilepsy ranges from 5-9/1000*
- Affects both ends of the age spectrum
- 0.5-1% of paediatric population have epilepsy
- Rates of epilepsy highest during first year of life and then decline with age

*Hauser et al. Epilepsia 1991
In Victoria

- Children with seizures comprise 25% of paediatric consultations (*Barwon Paediatric Group data*)
- RCH sees 800 children with epilepsy per year
- Comprises 50% of paediatric neurology consultations in the Department of Neurology
The Three Big Questions

• Was it a really a seizure?

• What type of seizure?

• What is the epilepsy syndrome?
Was it really a seizure?
Non Neurological Causes

• Normal physiological phenomenon
  – Jitteriness
  – Sleep Myoclonus

• Exaggerated physiologic
  – Startle
  – Benign Myoclonus of Infancy

• Behavioural
  – Shuddering
  – Daydreaming
  – Masturbation

• Psychiatric
  – Pseudoseizures
  – Panic Attacks
Was it really a seizure?
Non Neurological Causes

• Parasomnias / Sleep disorders
  – Night terrors
  – Sleep walking
  – Narcolepsy/Cataplexy
• Breatholding
  – Cyanotic
  – Pallid
• Syncope
  – Cardioneurogenic
  – Reflex
  – Orthostatic
  – Congenital Heart Disease (Aortic Stenosis, Tetralogy)
  – Arrhythmias
• Metabolic
Was it really a seizure? Neurological Causes

• Cerebrovascular Disorders
  – Ischaemic stroke
  – Intracranial haemorrhage

• Migraine

• Migraine variants (channelopathies)
  – Benign Paroxysmal Torticollis of Infancy
  – Benign Paroxysmal Vertigo / Vertebrobasilar Migraine
  – Confusional Migraine
Was it really a seizure?

Neurological Causes

• Movement disorders
  – Tics
  – Tremor
  – Paroxysmal Dystonias
  – Paroxysmal Choreoathetosis
  – Opsoclonus Myoclonus
  – Hyperekplexia
Classification of Afebrile Seizures

SEIZURE

Provoked?

YES

Acute Provoked

NO

One only

More than one

Solitary Seizure

Epilepsy
“First” Afebrile Seizure

- Distinguish between provoked and unprovoked attacks

- Immediate provoking causes:
  - CNS trauma, tumor, metabolic, poisoning

- Is it the first unprovoked afebrile seizure?

- The 2 year recurrence risk after an unprovoked first afebrile seizure is around 40%

- Unrecognised seizures may have preceded the “Index” seizure (52% in CAROLE study)*

Classification of Epileptic Seizures and Syndromes in Children

• Confusing terminology and imprecise classification
• Expanding list of epilepsy syndromes and aetiologies
• Why attempt to classify?
  – Aids in choice of investigations
  – Determines choice of medical and surgical therapies
  – Aids in counselling regarding prognosis
  – Important to have a framework for research
ILAE Classification of Epileptic Seizures and Syndromes

Epileptic Seizure Type

Generalised

Focal

Epilepsy Syndrome

Idiopathic

Symptomatic

Idiopathic

Idiopathic Generalised Epilepsy (IGE)

Idiopathic Focal Epilepsy (IPE)

Symptomatic

Symptomatic Generalised Epilepsy (SGE)

Symptomatic Focal Epilepsy (SPE)

Proposal for revised clinical and electroencephalographic classification of epileptic seizures


Proposal for revised classification of epilepsies and epileptic syndromes

Epilepsia 1989;30:389-99
A Proposed Diagnostic Scheme for People with Epilepsy (ILAE Task Force)*

Axis 1: ictal phenomenology
Axis 2: seizure type (inc. localisation, precipitants)
Axis 3: syndrome
Axis 4: aetiology
Axis 5: impairment

* A Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy
Epilepsia 2001;42:1-8
The new classification system

- Delineates the epilepsies with respect to aetiologies and the specificity of diagnosis

- Encompasses
  - electroclinical syndromes
  - non-syndromic epilepsies with structural-metabolic causes
  - epilepsies of unknown cause.
Epileptic Seizure Types

- Division into three broad categories based on clinical features (semiology) and EEG findings
  - Generalised seizures
  - Focal seizures
  - Unknown (includes epileptic spasms)

- Changes to previous classification system
  - Neonatal seizures no longer recognised as a separate entity
Generalised seizures

- Seizures originating at some point within and rapidly engaging bilaterally distributed networks
- Can involve cortical and subcortical structures but not necessarily the entire cortex
- Can appear localised or lateralised but without consistency from one seizure to another
- Can be asymmetric
Generalised seizures

- Tonic-Clonic
- Clonic
- Tonic
- Epileptic Spasms
- Absence
  - Typical absence
  - Atypical Absence
  - Myoclonic Absence
  - Eyelid myoclonia

- Myoclonic
  - Myoclonic
  - Myoclonic-atonic
  - Myoclonic-tonic

- Atonic (astatic)
Focal (=partial) seizures

- Seizures originating within networks of one hemisphere
- Ictal onset is consistent from one seizure to the next
- The distinction between simple and complex partial seizures abandoned
Focal Seizures

- **Simple Partial**
  - Consciousness is preserved during the seizure
  - Focal motor
  - Somatosensory or special sensory symptoms
  - Autonomic symptoms
  - Psychic symptoms

- **Complex Partial**
  - Usually associated with loss of consciousness

- **Secondarily Generalised Seizures**
Semiological classification of focal seizures

- Focal Sensory Seizures
  - Elementary
    - Tingling, numbness
  - Experiential
    - Déjà vu
    - Derealisation
    - Depersonalisation

- Focal Motor
  - Clonic
  - Asymmetrical Tonic
  - Automatisms
  - Hyperkinetic

- Gelastic

- Hemiclonic

- Secondarily Generalised
History - Important Questions

• Were there precipitating factors?
  – Lack of sleep, illness, fever, stress

• Were seizures preceded by an aura?
  – sensory, auditory, visual, autonomic

• Was awareness preserved during the seizure?

• Were there any focal features?
  – automatisms, focal tonic posturing, clonic jerking
  – Head or eye deviation

• Lateralised post ictal weakness?
Examination Findings

- Focal neurological findings
- Organomegally
- Neurocutaneous stigmata
- Dysmorphic features
Generalised Seizures

• Tonic-Clonic
• Clonic
• Tonic
• Epileptic Spasms
• Absence
  – Typical absence
  – Atypical Absence
  – Myoclonic Absence
  – Eyelid myoclonia

• Myoclonic
  – Myoclonic
  – Myoclonic-atonic
  – Myoclonic-tonic

• Atonic (astatic)
Generalised Tonic Clonic Seizures

- Loss of consciousness at onset

- Tonic posturing (decorticate then decerebrate) due to sustained muscle contraction

- Gradual evolution into rhythmic clonic jerking (recurrent inhibition of tetanic contraction)

- Post ictal depression of consciousness and cortical metabolic function

- **MPG Videos\generalised tonic clonic.mpg**
Tonic Seizures

- Sudden stiffening of all muscle groups, especially trunk and upper body
- Associated with apnoea
- Often occur during sleep, usually last 10-15 secs
- Short post ictal period

- EEG usually shows
  - flattening (decrement)
  - generalised fast activity

- Most often seen symptomatic generalised epilepsies

MPG Videos\tonic.mpg
Atonic Seizures

- Sudden loss of muscle tone with falling
  - “head nod” or “drop attack”

- EEG shows generalised fast activity, or poly spike-slow wave activity

- Seen in both symptomatic and idiopathic generalised epilepsies

- Videos\atonic.avi
Differential Diagnosis – Non-epileptic

- MPG Videos\stretch syncope.mpg
- MPG Videos\breath-holding.mpg
- MPG Videos\pseudoseizure.mpg
- Videos\cataplexy.avi
Myoclonic Seizures

- Brief, shock like involuntary muscle contractions due to cortical epileptic discharges

- Can be generalised, focal, multifocal, symmetrical or asymmetrical

- Can also have negative myoclonus from muscular inhibitions

- EEG correlate of high amplitude polyspike-slow wave discharges

- **MPG Videos\myoclonic jerks.mpg**
- **Videos\negmyoclonicaton ic.avi**
Differential Diagnosis – Non-epileptic

- MPG Videos\sleep jerks.mpg
- Videos\abnormalstartle.avi
Typical Absence Seizures

- Sudden onset with NO warning
- Brief episodes of staring lasting 5-45 seconds
- Can be associated with
  - Oral and manual automatisms
  - Clonic movements
  - Atonic or tonic components
- Activated by hyperventilation
- EEG shows
  - 3 Hz spike-wave in CAE
  - > 4 Hz spike-wave in JAE

MPG Videos\absence.mpg
Differential Diagnosis – Non-epileptic

- MPG Videos\day dreaming.mpg
- MPG Videos\day dreaming and wave.mpg
Semiological classification of focal seizures

• Focal Sensory
  – Elementary
    • Tingling, numbness
  – Experiential
    • Déjà vu
    • Derealisation
    • Depersonalisation
  – Autonomic

• Focal Motor
  – Clonic
  – Asymmetrical Tonic
  – Automatisms
  – Hyperkinetic
Focal seizures with motor symptoms

- Semiology depends on seizure onset and spread within somatotopically organised motor cortex
- Consciousness preserved (awareness, responsiveness)
- Can have a “Jacksonian march”

Videos\focal13.avi
Focal seizures with sensory symptoms

• Somatosensory (Parietal Lobe Seizures)
  – Pins and needles, dysaesthesia or an electric shock
  – numbness

• Special sensory symptoms
  – Visual
    • Simple visual hallucinations
    • Complex (structured) visual phenomenon
  – Olfactory
  – Gustatory
  – Auditory
Focal seizures of temporal lobe origin

- Characterised by behavioural arrest, staring, unresponsive and oromotor automatisms

- Can be associated with ipsilateral head version, contralateral dystonic posturing

- May be preceded by an aura
  - epigastric, olfactory, auditory, autonomic or psychic symptoms

- **MPG Videos\CPS temporal.mpg**
Focal seizures of frontal lobe origin

- Characteristically hyperkinetic seizures, axial movements, vocalisation, and bilateral gestural automatisms
- Rapid Secondary generalisation
- Often nocturnal
- Brief duration
- Minimal post ictal confusion

[MPG Videos\CPS frontal awake.mpg]
Secondarily Generalised Focal Seizures

• MPG Videos\SGS.mpg
**Differential Diagnosis – Non-epileptic**

- Videos\masturbation.avi
- MPG Videos\simpetic.mpg
- Videos\tourette.avi
- Videos\shuddering.avi
Epilepsy Syndromes in Children

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Proposed Diagnostic Scheme for People with Epilepsy
(ILAE Commission 2001)

Axis 1: ictal phenomenology
Axis 2: seizure type (inc. localisation, precipitants)
Axis 3: syndrome
Axis 4: aetiology
Axis 5: impairment
ILAE Classification of Epileptic Seizures and Syndromes

Epileptic Seizure Type

Generalised

Focal

Epilepsy Syndrome

Idiopathic

Symptomatic

Idiopathic

Symptomatic

IEG

IPE

SGE

SPE

Proposal for revised clinical and electroencephalographic classification of epileptic seizures

Revised terminology and concepts for organization of seizures and epilepsies (2010).

- Move away from use of terms idiopathic, cryptogenic, symptomatic, benign
  - Idiopathic has previously implied a good outcome
  - All epilepsy is symptomatic but some is genetic and some is due to identifiable structural pathology or metabolic disorders
  - Cryptogenic is not used consistently and has been abandoned, now considered as unknown
  - Self limited and pharmacoresponsive better terms than benign
Disease vs. Syndrome: Levels of specificity

• Electroclinical syndromes
  – Restricted to entities with a combination of typical age onset, specific seizure types and EEG patterns

• Constellations
  – Clinically distinct constellations based on specific lesions or causes
  – Epilepsies associated with structural lesions or metabolic conditions

• Epilepsies of unknown cause (at least 1/3rd of all cases)
Electroclinical epilepsy syndromes

Organised by age of onset
This includes epilepsies due to genetic or presumed genetic disorders
Paediatric Electroclinical Epilepsy syndromes

- Neonatal onset
  - Benign familial neonatal epilepsy
  - Early Myoclonic Encephalopathy
  - Ohtahara Syndrome (EIEE)

- Infantile Onset
  - Benign Familial Infantile Epilepsy
  - Benign Partial Seizures of Infancy
  - West syndrome
  - Severe Myoclonic Epilepsy of Infancy (Dravet Syndrome)
  - Migrating Partial Epilepsy of Infancy

- Early Childhood (Preschool) Onset
  - Panayiotopoulos type early onset childhood occipital epilepsy
  - Epilepsy with Myoclonic Absences
  - Epilepsy with Myoclonic Atonic Seizures (Doose Syndrome)
  - Lennox Gastaut Syndrome
  - Landau Kleffner Syndrome
  - Epileptic encephalopathy with Continuous Spike Wave in Slow Wave Sleep (CSWS)
  - Hypothalamic Hamartoma Syndrome
  - Febrile seizures+

- Later Childhood and Adolescence
  - Childhood Absence Epilepsy
  - Benign Focal Epilepsy of Childhood with Centroparietal Spikes
  - Gastaut type late onset childhood Occipital Epilepsy
  - Juvenile Absence Epilepsy
  - Juvenile Myoclonic Epilepsy
  - Autosomal Dominant Frontal Lobe Epilepsy
  - Autosomal Dominant epilepsy with auditory features
  - Other familial temporal lobe epilepsies
Early Childhood Epileptic Encephalopathies

- Syndrome associated with a high probability of encephalopathic features that develop or worsen after onset of the epilepsy
- Demonstrate a failure to develop at an expected rate relevant to same aged peers.

- Onset in Neonatal Period
  - Ohtahara Syndrome
  - Early Myoclonic Encephalopathy

- Onset in Infancy
  - Infantile Spasms (West Syndrome)
  - Severe Myoclonic Epilepsy of Infancy (Dravet Syndrome)

- Onset in Early Childhood
  - Lennox Gastaut Syndrome
Infantile Spasms

- Triad of infantile spasms, hypsarrhythmia and arrest of psychomotor development
- Age specific epilepsy syndrome
- Age dependent of response to multiple aetiologies
- Estimated incidence of 0.25-0.60 per 1000 live births
- Peak age of onset between 3-7 months, >95% have onset before age 2
- 61-93% are “symptomatic” in recent studies, further divided into pre-, peri- and postnatal causes.
- Usually associated with a structural CNS abnormality
Infantile Spasms

- Spasms can be flexor (salaam) extensor (cruciate) or mixed

- Can be asymmetrical or have focal features

- Typically occur in clusters 5-30 seconds apart

- Frequently occur on waking

- Can be associated with other seizures types

- EEG demonstrates hypsarrhythmia

- “Electrical chaos”

- Videos\infantilespasms. avi
Severe Myoclonic Epilepsy of Infancy (Dravet Syndrome)

- Onset of frequent, prolonged hemiclonic or generalised febrile convulsions in the first year of life
- Subsequent appearance of afebrile focal, hemiclonic, myoclonic, GTC seizures
- Environmental temperature sensitivity, photic sensitivity
- Developmental regression and ataxia in the 2nd and 3rd years of life
- EEG initially normal but appearance of multifocal and generalised polyspike wave activity in the second yr
- Mutations in SCN1A, SCN1B, SCN2A, GABRGG2 genes
Electroclinical epilepsy syndromes of early to mid childhood
Childhood Absence Epilepsy

- 2-8% of patients with epilepsy
- 30% of children have positive family history
- Onset between ages 3-12 yrs, peak at 6-7 yrs
- EEG shows bisynchronous 3 Hz spike wave
- Induced by hyperventilation
- Up to 40% can have GTCS during adolescence
- Seizures remit in 80% with treatment
Benign Focal Epilepsy of Childhood with CTS

- The most common single form of epilepsy and the most common epileptic EEG pattern in childhood
- Peak age of onset 7-9 years

- Sleep related seizures
  - simple partial hemimotor seizures, with sensory symptoms, drooling, anarthria
  - hemiconvulsion or 2° GTCS

- EEG unilateral or independent bilateral sharp-slow with a tangential dipole in the low central region, activated by sleep

- Universal seizure remission
- during puberty, normal
- Development
- Videos\BFEC2.avi
Lennox Gastaut Syndrome

- 2-3% of all childhood epilepsies
- M>F, 1.5:1, peak age of onset 3-5 years
- Can evolve into LGS from IS but 25-30% are previously normal children
- Triad of
  - Generalised seizures-tonic, atypical absence, atonic
  - Interictal EEG pattern of “slow spike wave”
  - Diffuse cognitive dysfunction (mental retardation)
- Frequently associated with non-convulsive status epilepticus
Myoclonic Astatic Epilepsy

• Onset between 1-8 yrs in previously normal children
• Myoclonic and myoclonic astatic seizures due to axial and proximal limb involvement
• Fall because of
  – massive myoclonic jerk (Spike corresponds with EMG burst)
  – post myoclonic inhibition (slow wave corresponds with silent period on EMG)
• Other seizure types: tonic-clonic>absence> status
• Paroxysmal 4 Hz theta bursts, fast generalised spike and polyspike wave, photosensitivity
• Variable prognosis
• CMVideo00012CACA.avi
Idiopathic Occipital lobe epilepsies of Childhood

Panayiotopoulos syndrome
- Earlier onset
- Prominent autonomic symptoms
  - vomiting, pallor, salivation
- Head and eye version
- Consciousness impaired
- Seizures infrequent but focal
  status epilepticus is a common phenomenon
- Sleep associated seizures
- 25% single seizure and remission highly likely
- EEG: Occipital or multifocal DC
- MPG Videos\SPS visual.mpg

Gastaut syndrome
- Later onset
- Elementary visual hallucinations
  - multicoloured and circular
- Ictal blindness
- Tonic deviation of eyes, nystagmus, eyelid fluttering
- Ictal vomiting uncommon
- Consciousness preserved
- Seizures more frequent but short duration
- Diurnal seizures
- Remission less likely
- Focal occipital discharges with fixation off sensitivity
Get the child to draw the visual symptoms

I can see Mum when she’s not in the room.

This is what I see when I have my eyes open.
Electroclinical epilepsy syndromes of later childhood and adolescence
Juvenile Absence Epilepsy

- Onset after age 10yrs (2nd peak age of onset)
- Absences relatively infrequent but longer duration
- Often occur on waking
- Generalised tonic clonic seizures more common
- Myoclonic seizures occur in 15%
- EEG shows fast (poly) spike wave discharges
- Induced by hyperventilation
Juvenile Myoclonic Epilepsy

- Onset of jerks at 12-18 yrs
- Strong genetic predisposition, accounts for about 10% of all epilepsies
- Early morning myoclonus often goes unrecognised, triggered by fatigue, sleep deprivation and alcohol
- Can present as a generalised tonic clonic convulsion on waking
- EEG shows fast (poly) spike-wave discharges
- Usually excellent response to sodium valproate but is a life long condition
Generalised Tonic Clonic Seizures on Waking

Juvenile Myoclonic Epilepsy

Juvenile Absence Epilepsy

Generalised Tonic-Clonic Seizures on Waking
Distinctive constellations
Underlying causes

• Genetic
  – Diagnosis is the direct result of a known genetic or presumed genetic defect
  – Knowledge may be derived from specific molecular genetic studies or well designed family studies

• Structural metabolic
  – Distinct structural or metabolic condition which has been demonstrated to be associated with a substantially increased risk of epilepsy

• Unknown causes—nature of the underlying cause is as yet unknown
Focal seizures originating from the temporal lobe due to hippocampal sclerosis
Gelastic seizures due to hypothalamic harmatoma

- Onset often in the neonatal period
- Paroxysmal laughing episodes which occur suddenly and out of context
- Can also have crying (dacrystic) seizures
- Often associated with precocious puberty
Epilepsies due to structural causes:
Focal Cortical Dysplasia
Epilepsies due to neurocutaneous disorders

Tuberous sclerosis

Sturge Weber Syndrome
Malformations of cortical development and Genes

- Tuberous sclerosis
  - TSC-1 (AD Harmartin Chr 9) and TSC-2 (AD Tuberin Ch 16)
- Lissencephaly-pachygyria
  - Classical LIS1 (AR), DCX (XLR)
  - Others ARX (XLR), RELN (AER)
- Subcortical band heterotopia
  - DCX
- Periventricular nodular heterotopia
  - FLNA (XLR Filamin 1), ARFGEF2 (AR)
- Bilateral Perisylvian Polymicrogyria
  - GPR56, 22q deletion syndromes
Epilepsies due to major cerebral malformations

- lissencephaly
- schizencephaly
- hemimegalencephaly
Acquired structural aetiologies

- **Perinatal**
  - HIE, Porencephaly

- **Postnatal**
  - Encephalitis
  - Meningitis
  - TORCH
  - Trauma
  - Tumours
  - Stroke
  - Haemorrhage
Epilepsies due metabolic disorders

• Metabolic Disorders “Small Molecule”
  – Organic acidurias,
  – Amino acidopathies,
  – Urea cycle defects
  – Mitochondrial Disorders
  – Vitamin responsive epilepsies
    • B6, Folate, Biotin

• Neurodegenerative disorders
  – Lysosomal disorders-MLD, gangiosidosis, sialidosis
  – Neuronal Ceroid lipofuscinosis
  – Progressive myoclonic epilepsies
Mitochondrial clinical syndromes
genotypes and phenotypes

Common mtDNA mutations

- Kearns-Sayre syndrome (KSS)
- Mitochondrial encephalomyopathy, lactic acidosis, and stroke like episodes (MELAS)
- Myoclonic epilepsy with ragged-red fibers (MERRF)
- Leber’s hereditary optic neuropathy (LHON)
- Neuropathy, ataxia and retinitis pigmentosa (NARP)
- Maternally inherited Leigh disease
Figure 1. The mitochondrial respiratory chain, showing nDNA-encoded (light-shaded) and mtDNA-encoded (dark-shaded) subunits. Protons (H+) are first pumped from the matrix to the intermembrane space through Complexes I, III, and IV. They are then pumped back into the matrix through Complex V to produce ATP. Coenzyme Q (CoQ) and cytochrome c (Cyt c) are electron transfer carriers.
Alpers syndrome

- Autosomal recessive hepatocerebral degenerative disorder.
- Affected individuals usually present in early childhood developmental regression, seizures and ataxia.
- Liver dysfunction can present at any stage during the child’s life and may progress to liver failure in the terminal phase of the disease.
- Children with Alpers syndrome do not usually survive beyond the 2nd decade of life and the majority die in the first decade 10 years of age.
- Brain biopsy shows neuronal loss, glial proliferation and spongiosis.
- Respiratory chain enzyme analysis may show low complexes I, III and IV oxidative phosphorylation enzymes.
- Liver and muscle EM shows depletion of mitochondrial DNA.
Mitochondrial DNA polymerase gamma (POLG) mutations have been recognised as the cause of Alpers syndrome (Naviaux and Nguyen 2004).

3 Common mutations identified

POLG mutations can be associated with a range of other clinical syndromes including ataxia, progressive external ophthalmoplegia (PEO), parkinsonism and premature ovarian failure, psychiatric illness.
Pyridoxine Dependent Epilepsy

• Autosomal recessive disorder with prevalence of 1:400,000-700,000
• Early onset epileptic encephalopathy
• Typically presents with seizures soon after birth, but may be later
• EEG varies from multifocal abnormalities to suppression burst
• Consider in differential for
  – preterm infants with HIE
  – Idiopathic refractory seizures, with onset ~first year of life
Pyridoxine Dependent Epilepsy

- Defect in α-amino adipic semialdehyde (AASA) dehydrogenase
- Increased AASA (specific) and pipecolic acid (non-specific) in urine, plasma and CSF (even on treatment)
- Due to mutation in the antiquitin gene (ALDH7A1)
- Important to diagnose early because
  - Outcome may be better with early recognition and correct treatment
  - Allows weaning of other anticonvulsants
  - Intrauterine treatment can prevent seizures
  - Genetic counselling
When AASDH (*antiquitin*) activity is deficient, pipecolic acid and P6C both accumulate. P6C sequesters P5P, the biologically active form of pyridoxine. The conversion of pyridoxine into P5P is catalyzed by PNPO.
Vitamin trials

- Pyridoxine 100mg/kg iv or orally followed by 30mg/kg daily for 3 days (max 200-300mg/day)

- If ineffective: PLP 30-50mg/kg/d tds (similar caution with apnoea to pyridoxine), continue for 3 days

- If ineffective: Add on therapy with folinic acid 3-5mg/kg/d
Folinic Acid–Responsive Seizures Are Identical to Pyridoxine-Dependent Epilepsy

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**Objective:** Folinic acid–responsive seizures and pyridoxine-dependent epilepsy are two treatable causes of neonatal epileptic encephalopathy. The former is diagnosed by characteristic peaks on cerebrospinal fluid (CSF) monoamine metabolite analysis; its genetic basis has remained elusive. The latter is due to α-aminoacidic semialdehyde (α-AASA) dehydrogenase deficiency, associated with pathogenic mutations in the ALDH7A1 (antiquitin) gene. We report two patients whose CSF showed the marker of folinic acid–responsive seizures, but who responded clinically to pyridoxine. We performed genetic and biochemical testing of samples from these patients, and seven others, to determine the relation between these two disorders.

**Methods:** CSF samples were analyzed for the presence of α-AASA and pipecolic acid. DNA sequencing of the ALDH7A1 gene was performed.

**Results:** Both patients reported here had increased CSF α-AASA, CSF pipecolic acid, and known or likely pathogenic mutations in the ALDH7A1 gene, consistent with α-AASA dehydrogenase deficiency. Analysis of CSF samples from seven other anonymous individuals diagnosed with folinic acid–responsive seizures showed similar results.

**Interpretation:** These results demonstrate that folinic acid–responsive seizures are due to α-AASA dehydrogenase deficiency and mutations in the ALDH7A1 gene. Thus, folinic acid–responsive seizures are identical to the major form of pyridoxine-dependent epilepsy. We recommend consideration of treatment with both pyridoxine and folinic acid for patients with α-AASA dehydrogenase deficiency, and consideration of a lysine restricted diet. The evaluation of patients with neonatal epileptic encephalopathy, as well as those with later-onset seizures, should include a measurement of α-AASA in urine to identify this likely underdiagnosed and treatable disorder.

Glucose Transporter Defect

• In children, the brain glucose demand is 3-4 times higher than that of adults (up to 80% of whole body glucose utilisation).

• GLUT1 is expressed in two isoforms, one in the luminal and albuminal membranes of brain capillaries; BBB and the other in all other neural cells.

• GLUT1 is also the predominant glucose transporter in erythrocytes.
Genetics and pathophysiology

- AD, but often a result of a *de novo* gene mutation.
Clinical presentation

- Seizures are classically the first manifestation. Onset: usually 1-4 months.
- Other episodic or paroxysmal non-epileptic events or phenomena occur.
- Often related to fatigue and hunger, usually before meals.
- Most often:
  - Abnormal episodic eye movements
  - Intermittent ataxia
  - Dystonia
  - Alternating hemiparesis
  - Sleep disturbance
  - Dysarthria
- Acquired microcephaly or more often, deceleration of head growth
Diagnosis

• Paired CSF/serum glucose:
  – Normal average ratio ~ 0.6
  – In GLUT1-DS ratio ranges 0.19-0.46 (average value 0.33)
  – Remember that CSF cell count, protein and blood glucose levels are normal.

• Absolute CSF glucose typically <2.2mmol/L

• CSF lactate: low or low-normal.

• Genetic testing now available-mutation in the SLC2A1 gene
Useful resources

- Epilepsy Australia: www.epilepsyaustralia.org
- Epilepsy Action Australia: www.epilepsy.org.au
- Children’s Epilepsy Program
  www.rch.org.au/cep
- American Epilepsy Society
  www.aesnet.org
Syndromal Classification: Idiopathic Epilepsies

- “A disorder unto itself” with no identifiable cause
- Implies a genetic predisposition to seizures
- Predictable age of onset
- Characteristic EEG abnormalities
- “Channelopathies”
- Cryptogenic refers to conditions where the seizures are presumed to be symptomatic but the cause has not yet been identified
Syndromal Classification: The Symptomatic Epilepsies

• Seizures are secondary to an underlying brain abnormality

• Disorders of cortical development
  – Focal Cortical Dysplasia
  – Hemimegalencephaly
  – Lissencephaly
  – Periventricular /band heterotopias
  – Polymicrogyrias
  – Schizencephaly
ILAE Classification of Epileptic Seizures and Syndromes

Epileptic Seizure Type

<table>
<thead>
<tr>
<th>Epilepsy Syndrome</th>
<th>Generalised</th>
<th>Focal</th>
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</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>IGE</td>
<td>IPE</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>SGE</td>
<td>SPE</td>
</tr>
</tbody>
</table>

Proposal for revised clinical and electroencephalographic classification of epileptic seizures


Symptomatic generalised epilepsy

- Tonic and atonic seizures characteristic
- Lennox Gastaut the prototype
- Brainstem mediated
- Characteristic EEG patterns-paroxysmal fast and decrements
- Refractory to Rx
- AEDs, KD and VNS
Afebrile Seizures in Children

• The most important question in the ED assessment of children with seizures

IS IT A SEIZURE?

• Distinguish between epileptic and non epileptic events
Goals of Immediate Evaluation

• What type of seizure is it?

• What is the cause?
  – Idiopathic
  – Symptomatic from remote insult

What further investigations are required?
First Afebrile Seizure: Utility of Diagnostic Tests

• AAN Practice Parameter-Evidence Based review
  – Class I: Prospective cohort with adequate sample size.
  – Class II: Retrospective or prospective with inadequate sample size
  – Class III: Small cohort/ case report/ expert opinion
• Standard, Guideline, Option
Laboratory Studies

• FBC, Electrolytes, BUN, Creatinine, Glucose, Calcium, Magnesium, Toxicology
  – Abnormalities rarely found (except in infants <6 months of age where up to 70 % have electrolyte disturbance)

PRACTICE OPTION, determine on individual clinical basis (i.e. vomiting, diarrhoea)
EEG- What’s the Evidence

• 10 Class I studies: - 4 showed abnormal EEG predictive of recurrence
• 54% chance of recurrence if EEG abnormal c.f. 25% chance if normal in one study (p<0.001)
• Activation procedures increase the yield
• Early (<24 hrs) vs. late – higher yield if done early? (54% v 34%)*
• Others believe lack sensitivity(61%), specificity(71%)**

• STANDARD OF CARE but optimal timing unclear

* King et al Lancet 1998;352:1007-11
** Gilbert et al Neurology 2000;54:635-641
Neuroimaging - What’s the Evidence

- CT: In 5 Class I and 14 Class II studies 2-11% had lesions that influenced management.
- MRI: 2 Class I studies, in one although 33% had abnormalities only 2% had lesions that influenced management.
- Issue of “Emergent” vs “non urgent”

Conclusions: PRACTICE OPTION
- MRI imaging investigation of choice
- Emergent if non resolving post ictal focal deficit
Acute seizure management

• Positioning to avoid injury during seizure
• Airway support
• Oxygen
• Use of rectal or intravenous benzodiazepines (0.2-0.5 mg/kg) if prolonged seizure (>5 minutes)
• Placing child in coma position following seizure
Management of Status Epilepticus

- Diazepam 0.2-0.5 mg I.V./P.R. and repeat
- Phenytoin 20 mg/kg IV + 5mg/kg +5 mg/kg
- Phenobarbitone 20 mg/kg + 5mg/kg +5 mg/kg

- Refractory Status epilepticus
- Midazolam infusion
- Thiopentone
Therapeutic Options

- Anticonvulsant medications
- Ketogenic diet
- Epilepsy surgery
- Vagal nerve stimulation
- No treatment
<table>
<thead>
<tr>
<th>Condition</th>
<th>Urine</th>
<th>Plasma</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridoxine/Folinic acid dependent</td>
<td>AASA Pipecolic acid</td>
<td>AASA Pipecolic acid</td>
<td>AASA Pipecolic acid</td>
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<tr>
<td></td>
<td>P6C</td>
<td>P6C</td>
<td>(peak X)</td>
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<tr>
<td>Hyperprolinemia II</td>
<td>AA (proline) P5C</td>
<td>AA (proline) P5C</td>
<td>AA (proline) P5C</td>
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<tr>
<td>Pyridoxine 5’ phosphate oxidase (PNPO)</td>
<td>VLA peak</td>
<td>AA (raised threonine and glycine, low arginine) Lactate PLP</td>
<td>AA (raised threonine and glycine, low arginine) PLP</td>
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<td>Cong hypophosphatasia</td>
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<td>Bone profile</td>
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