Uncontrolled Epilepsy

Epilepsies in which seizures are not adequately controlled by antiepileptic medication, or seizure control is possible only with intolerable side-effects.

- recurrent seizures (unpredictable, risks of injury & death)
- ineffective medications which cause side effects
- associated morbidity (physical, cognitive, psychiatric)
- impact on lifestyle (restrictions, community ignorance)
- socioeconomic costs (treatments, schooling, work)

~ 20% of children with epilepsy have uncontrolled seizures

Uncontrolled Epilepsies of Childhood

- some lesional partial epilepsies of childhood
  e.g. mTLE/HS, neocortical epilepsies 2^{o} FCD/TS/tumours, gelastic/HH
- some generalised epilepsies of childhood
  eg. Lennox-Gastaut syndrome, SMEI, various myoclonic epilepsies
- "catastrophic" infantile epilepsies
  eg. infantile spasms, Sturge-Weber, hemimegalencephaly, TS
- epileptic aphasia syndromes
  eg. Landau Kleffner syndrome, CSWS/ESES
- progressive neurological conditions
  eg. Rasmussen syndrome, progressive myoclonic epilepsies (NCLF)
- uncommonly, some idiopathic epilepsies
  eg. absence epilepsy, juvenile myoclonic epilepsy, atypical BFEC

Outcome for Uncontrolled Epilepsy

Intractable seizures can often be predicted by:

- accurate syndrome diagnosis
  eg. severe myoclonic epilepsy of infancy, symptomatic IS
- accurate aetiologic diagnosis eg. lesion on MRI
- lack of response to appropriate medication
  - only 11% patients with new-onset epilepsy and 1st drug efficacy failure became seizure free (Kwan & Brodie, NEJM 2000)

AED Resistant Epilepsy

- review diagnosis (? non-epileptic ? correct syndrome)
- remove triggers and modify lifestyle eg. IGE, reflex epilepsies
- check patient compliance (drug levels)
- use best AEDs for specific seizure type and syndrome
- remove AEDs potentially aggravating seizures
- use maximum tolerated doses +/- blood levels
- use "rational" AED combinations eg. VPA+LTG
- use new AEDs with greater efficacy, multiple actions or novel action eg. TPM, LEV
- consider "older" medications eg. PHT, PB, PRM
- change from preventative treatment to acute treatment of seizures or seizure clusters eg. oral/rectal BZPs

Treatments for AED Resistant Epilepsy

- review current diagnosis and treatment
- new antiepileptic drugs (clinical drug trials)
- epilepsy surgery
- vagal nerve stimulation
- deep brain stimulation
- ketogenic diet and other dietary therapies
- immunotherapies
- stereotactic radiosurgery eg. Gamma Knife
- behavioural therapies eg. biofeedback
- alternative therapies
- no treatment

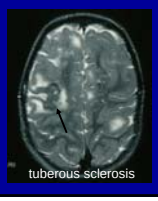
News Antiepileptic Drugs

acetazolamide
ACTH
brivaracetam
carbamazepine
chlorazepate
clonazepam
clobazam
diazepam
ethosuximide
felbamate
gabapentin
ganaxolone
immunoglobulins
lacosamide
lamotrigine
levetiracetam
lorazepam
midazolam
oxcarbazepine
paraldehyde
phenobarbitone
phenytoin
prednisolone
pregabalin
primidone
remacemide
rufinamide
stiripentol
sulthiame
tiagabine
topiramate
valproate
vigabatrin
zonisamide

Surgically-Remediable Syndromes

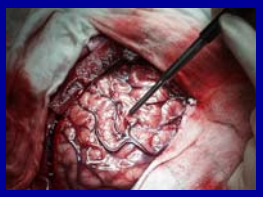
- focal lesional epilepsies
  - mesial TLE with hippocampal sclerosis
  - neocortical epilepsies 2° to tumours, cortical dysplasias/malformations, vascular m.
  - gelastic epilepsy and hypothalamic hamartoma
- hemispheric lesional epilepsies
  - unilateral SWS, PMG, HMG, schizencephaly
  - unilateral MCA territory infarct
  - chronic encephalitis (Rasmussen)
- multilesional, unifocal epilepsies
  - tuberous sclerosis
  - post traumatic/infective epilepsy
- some non-lesional epilepsies
  - neocortical partial epilepsies
  - Lennox Gastaut syndrome
  - Landau Kleffner syndrome


focal cortical dysplasia


tuberous sclerosis

Operations for Uncontrolled Epilepsy

- cortical resection
  eg. lesionectomy, corticectomy, lobectomy
- multilobar resection
- hemispherectomy
- corpus callosotomy
- multiple subpial transection
- stereotactic radiosurgery



Decreasing use of subdural EEG with improvements in neuroimaging.

Outcomes vary depending on syndrome and selection (~ 40-80% SF).

Presurgical Evaluation in Children with Epilepsy

- neurological assessment
  - detailed history (seizure characteristics and evolution, prior Rx)
  - focussed examination (neurocutaneous, subtle focal signs)
  - review of home video recording, previous EEG and MRI
- video-EEG monitoring +/- ictal SPECT
- high-resolution, “seizure-focussed” aMRI
- neuropsychological, family and PT/OT/ST assessments
- +/- other functional neuroimaging (eg. PET, fMRI etc)
  - → characterise and localise seizures
  - → determine underlying aetiology (lesion)
  - → assess impact of seizures and likely prognosis
  - → outline treatment (surgical) options

Vagal Nerve Stimulation

- consider in children with epilepsy who
  - failed appropriate AEDs
  - are not candidates for resective surgery
  - are being considered for callosotomy
  - may benefit from seizure termination
  - tonic drop attacks, recurrent status
- realistic expectations of efficacy
  - 50% have ≥50% seizure reduction
  - <10% chance of seizure freedom
  - stay on drugs
  - battery replacement after 5 years
- implications of failure
  - 2 operations, 2 scars, wire in-situ
  - $20,000 cost

Ketogenic Diet

A medically-supervised and strictly-regulated diet with restricted fluid, high fat, minimum protein and very low carbohydrate intake.

Classical (4 fat : 1 prot + CHO), MCT or modified MCT forms.

Body burns fat for energy (rather than carbohydrate and protein) and produces ketones ie mimics starvation & illness.

The brain can extract ß-hydroxybutyrate and acetoacetate and metabolise them separately to glucose.

KD raises seizure threshold but mechanism is unknown.

Ketogenic Diet - Indications

Indications
- some refractory childhood epilepsies
- pyruvate dehydrogenase deficiency
- glucose transporter defect

Contraindicated or caution in metabolic diseases with fat oxidation deficits and/or lactic acidosis
- pyruvate carboxylase deficiency
- carnitine deficiency
- mitochondrial disorders
- organic acidurias

Ketogenic Diet - Summary

- not a “natural” treatment or a “safe alternative” to drugs
- 1/3 marked improvement, 1/3 mild improvement, 1/3 none
- no difference in efficacy according to age or seizures
- medications are usually able to be reduced
- side effects are usually transient or reversible
- effects on cognition and behaviour have not been studied ? improved seizure control ? decreased medication ? Real
- caution with VPA because risk of mitochondrial dysfunction
- duration of treatment and long term effects uncertain
- no evidence that KD alters the natural history of epilepsy

Immunotherapies - treatments

- corticosteroids
  - ACTH (10-150 IU/day for 4-6 weeks)
  - hydrocortisone (10-25 mg/kg/day for 4-6 weeks)
  - prednisolone (various strategies)
  - methylprednisolone (10-15 mg/kg/day for 2-4 days)
- immunoglobulin (1g/kg/day for 2 days)
- Interferons
- monoclonal Abs
- plasma exchange

Immunotherapies - indications

- epileptic encephalopathies
  - West syndrome
  - Lennox Gastaut syndrome
  - epileptic-aphasia syndromes (LKS, ESES, EOS)
- “inflammatory epilepsies”
  - Rasmussen encephalitis
  - encephalitis/postencephalitis eg. HSVE, mycoplasma
  - seizures with ADEM
- refractory idiopathic epilepsy
  - refractory myoclonic or absence epilesy
  - atypical benign focal epilepsy
- status epilepticus of unknown aetiology in PICU

Potential Treatments for Uncontrolled Epilepsy

- **new AEDs** in RCT of chronic partial epilepsy
  - responder rates ~ 20-30%
  - seizure-free rates < 5-10%
- **ketogenic diet** in retro/prospective uncontrolled studies
  - responder rates ~ 30-50%
  - seizure-free rates ~ 10%
- **vagal nerve stimulation** in RCT and open studies
  - responder rates ~ 40-50%
  - seizure-free rates < 10%
- **surgery** in retrospective studies and one RCT
  - >90% reduction ~ 50-90%
  - seizure-free rates ~ 50-60%

Which Treatment for Which Refractory Syndrome

Syndrome	lesion	no lesion
febrile convulsions		
infantile spasms (West)	surgery	more AEDs & steroids, ketogenic diet
symptomatic partial epilepsy in infants	surgery	more AEDs, ketogenic diet
benign myoclonic epilepsy of infancy		
severe myoclonic epilepsy of infancy (Dravet)		more AEDs, STP, ketogenic diet, VNS
myoclonic astatic epilepsy (Doose)		**ketogenic diet**, steroids
childhood epileptic encephalopathy (Lennox Gastaut)	surgery	more AEDs, **VNS**, callosotomy
childhood absence epilepsy		**ketogenic diet**, steroids
benign occipital epilepsy (Panayatopoulos)		
benign rolandic epilepsy		more AEDs, **steroids**
acquired epileptic aphasia syndrome (Landau Kleffner)		more AEDs, **steroids**, MST
juvenile absence epilepsy		
juvenile myoclonic epilepsy (Janz)		more AEDs
IGE with TCS, photosensitive		
photosensitive epilepsy – generalised or occipital		
symptomatic partial epilepsies (TLE, FLE, etc.)	**surgery**	more AEDs, VNS