Pathophysiology, causes and treatment of tonic-clonic status epilepticus in adults

Epilepsy Society of Thailand
July 22nd 2010

Simon Shorvon

UCL Institute of Neurology, London UK

- Tonic clonic status epilepticus (SE)
- Pathophysiology
- Causes – common and uncommon
- The 3 stages of treatment of SE (excluding IV therapy)

Tonic-clonic status epilepticus

- Incidence approximately 18-36 cases per 100,000 persons per year. 0.1% of all A&E visits. Rates higher in children, learning disability, structural cerebral pathology, frontal pathology
- 65% of cases occur de novo, without prior history of epilepsy, due to acute cerebral event (vascular, trauma, infection) or acute metabolic/drug-induced cause
- In pre-existing epilepsy, TCSE is often precipitated by drug reduction/withdrawal, intercurrent illness, metabolic disturbance, progressive disease.
- SE occurs in 5% of all adults and 10-25% of all children with epilepsy
- Mortality rate – 10-20%

Pathophysiology of tonic-clonic SE – progressive changes

Premonitory stage

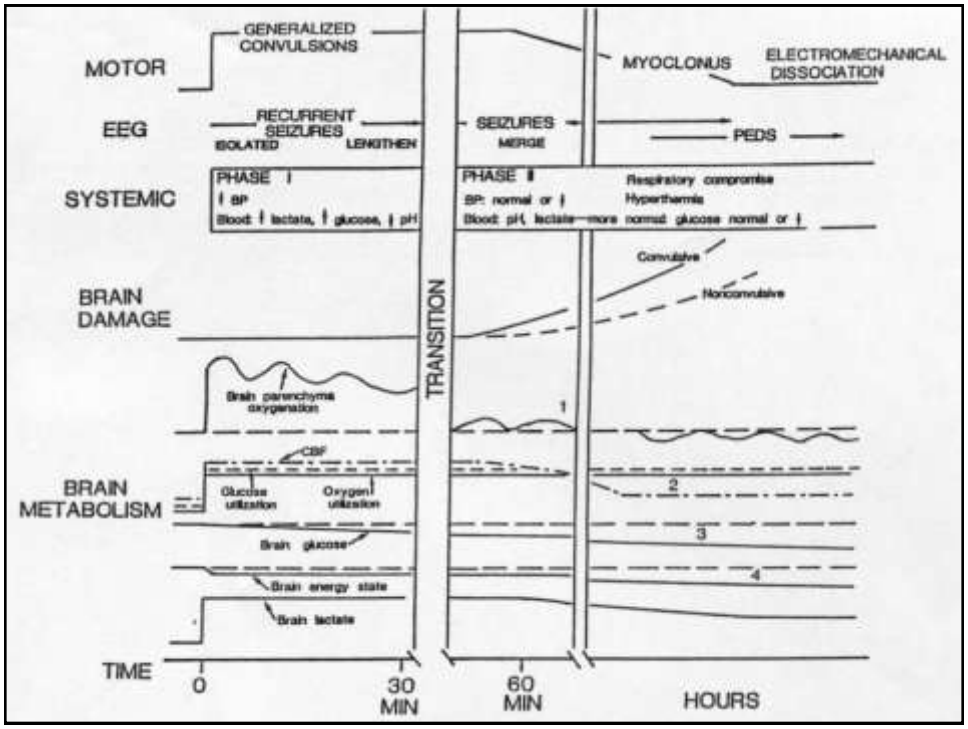
- Increasing serial seizures/myoclonus and EEG correlates

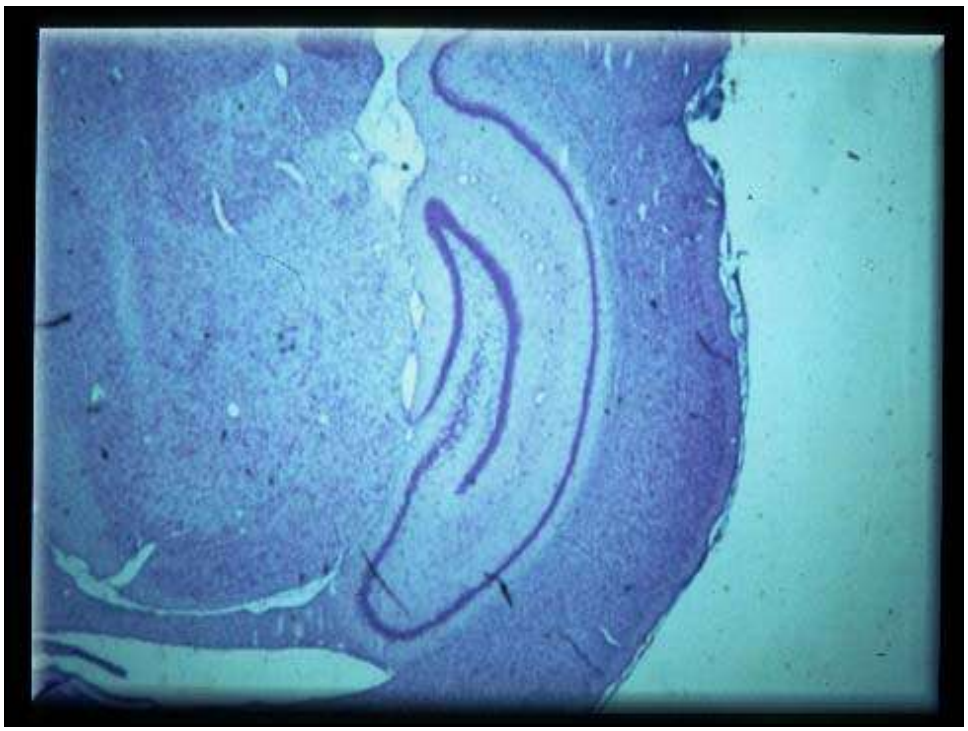
Biphasic pattern of physiological change

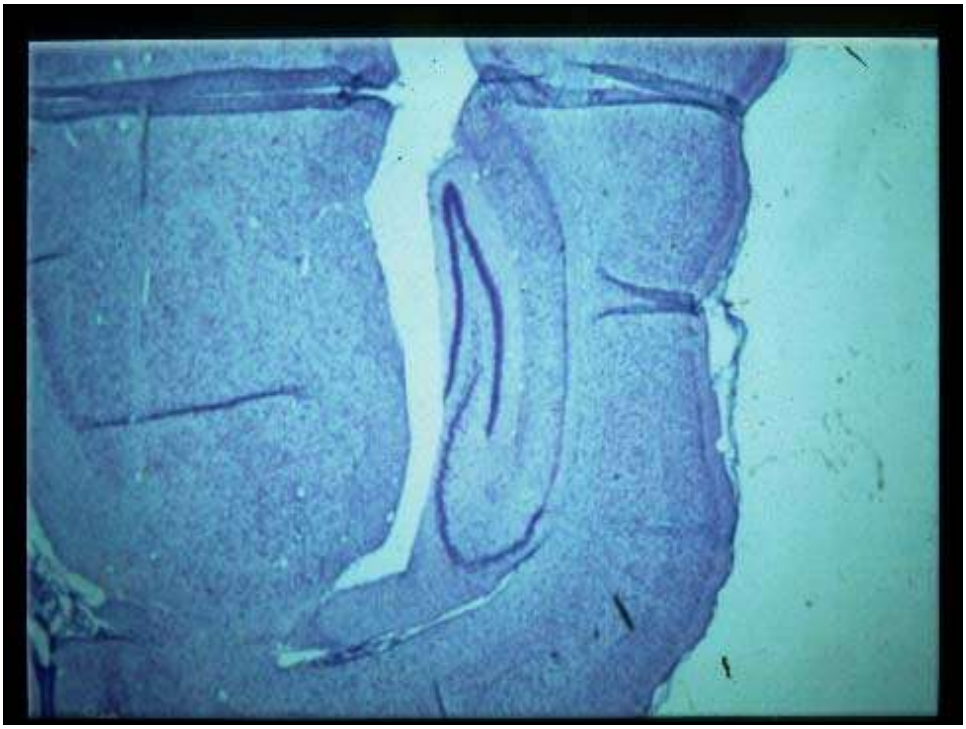
- Phase of compensation
- Phase of decompensation
- Reflected in progressive clinical and EEG changes
- Switch from compensated→decompensated state = 60-120 minutes in convulsive SE (an approximation, dependant on site, nature, severity of the SE)

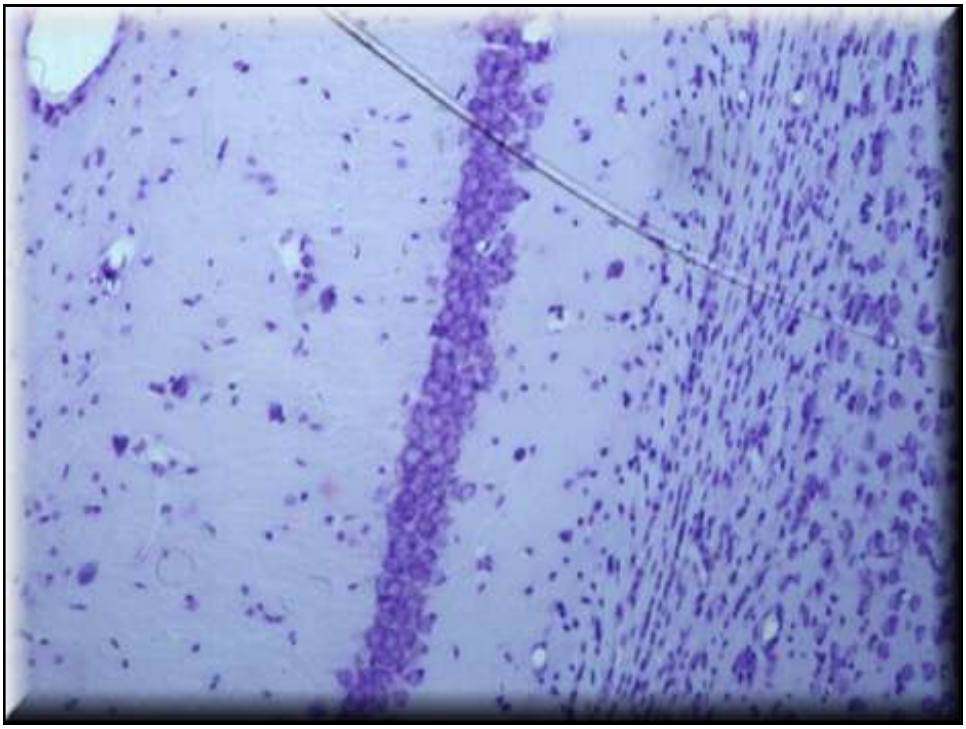
Window of opportunity for treatment

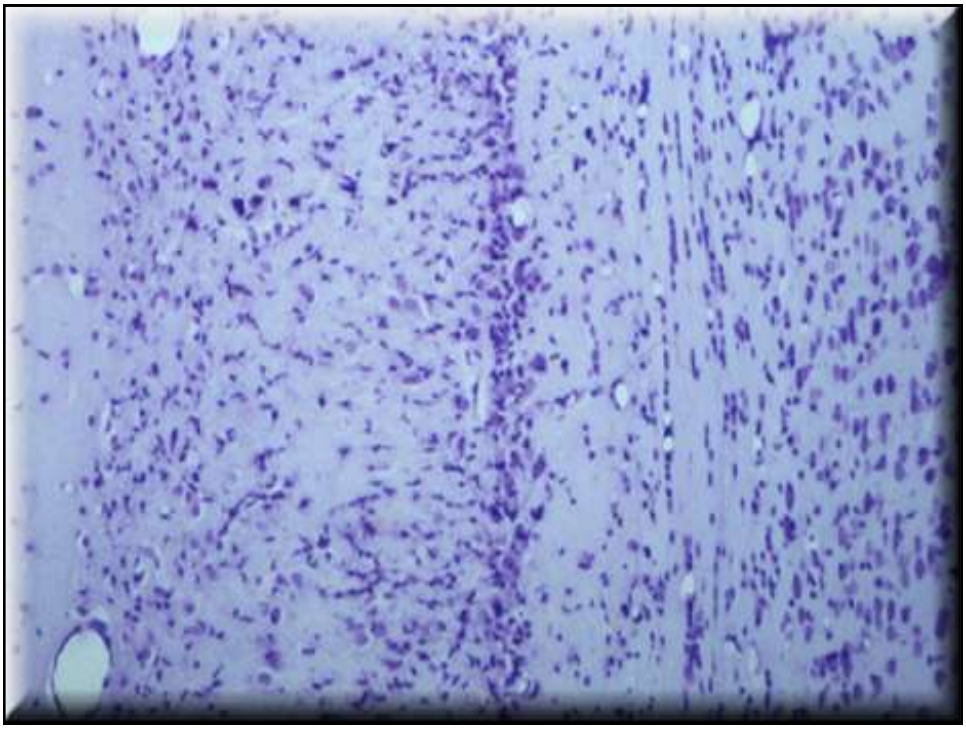
- Risk of cerebral damage increases with time after 60-120 mins – 'time is brain'
- Treatment failure increases with time


MOTOR
GENERALIZED CONVULSIONS
MYOCLONUS
ELECTROMECHANICAL DISSOCIATION
EEG
RECURRENT SEIZURES
ISOLATED
LENGTHEN
SEIZURES
MERGE
PEDS
SYSTEMIC
PHASE I
↓ BP
Blood: ↑ lactate, ↑ glucose, ↓ pH
PHASE II
BP: normal or ↓
Respiratory compromise
Hyperthermia
Convulsive
Nonconvulsive
BRAIN DAMAGE
TRANSITION
Brain parenchyma oxygenation
1
CBF
Glucose utilization
Oxygen utilization
2
BRAIN METABOLISM
3
Brain glucose
4
Brain energy state
Brain lactate
TIME
0
30 MIN
60 MIN
HOURS





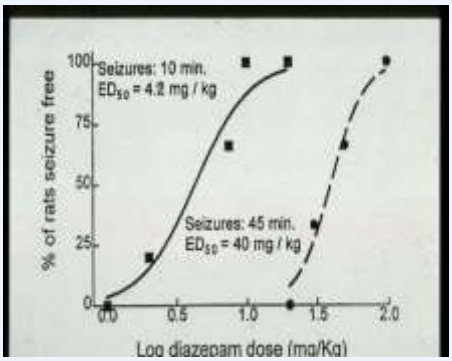




UCL

Some of the mechanisms of physiological change in SE

- **Calcium influx – causing excitotoxic cell death**
- **Change in gene expression (early and late) and change in protein action**
- **Histological change:**
  - **Synaptic re-org**
  - **Mossy fibre sprouting**
  - **Neurogenesis**
- **Receptor change: Trafficking/internalisation of GABAa receptors**



Causes of status epilepticus: common causes

	Rochester USA	Switzerland	Bologna Italy
Year	1965-84	1997-1998	1999-2000
Population	1,090,055	1,735,420	336,876
No. of cases	199	172	44
SE Incidence	18.3/100,000/yr	10.3/100,000/yr	13.1/100,000/yr
Prior epilepsy	44%	33%	39%
Acute sympt	50%	63%	34%
Remote sympt	20%	28%	34%
Idiopathic	14%		7%
Other/NK	**16%**	**9%**	**25%**

Causes of status epilepticus: common causes

- **Review of causes of SE in 1679 patients from 13 hospital series:**
  - **Infection** **9%**
  - **Cerebral tumour** **7%**
  - **Cerebrovascular disease** **10%**
  - **Trauma** **7%**
  - **Drugs, toxins, metabolic** **15%**
  - **Congenital/perinatal** **10%**
  - **Febrile SE** **12%**
  - **Other** **9%**
  - **Idiopathic/cryptogenic 19%**

Status was a presenting symptom in 59%, and an intercurrent event in 41%
(*Shorvon 1994*)

Uncommon causes in which SE is common or characteristic

Drug/toxin/metabolic
- Drug induced (Tiagabine, IV contrast agents, isonaizid)
- Toxin (Domoic acid, organophosphates, metals)
- Chromosomal disorders (ring chromosome 20, ring 14, Dup 15 etc)

Genetic / Chromosomal
- Ring chromosome 20 and other karyotype abnormalities
- Inherited metabolic disorders
- Cortical malformations (hemimegencephaly, others etc)
- Syndromes (Dravets, West etc)

Inflammatory/Infective
- Autoimmune/inflammatory 'neocortical encephalitis' (Rasmussen)
- Autoimmune/inflammatory 'limbic encephalitis'
- Infective (CJD, Tick-Borne Encephalitis, Cat scratch fever, etc)

Mitochondrial disease
- mtDNA defects – eg MELAS, MERFF, Leigh
- Nuclear gene mutations affecting mtDNA (*POLG1* gene Alpers' disease, occipital lobe epilepsy)

(Ep res 2010 in press)

Other drug induced Status epilepticus

- **Literature review**

  Over 100 reports of drug-induced SE
  Small case series/ reports; there is no systematic study
  More than 10 reports = +++
  SE less than 4% in large series of drug-induced szs

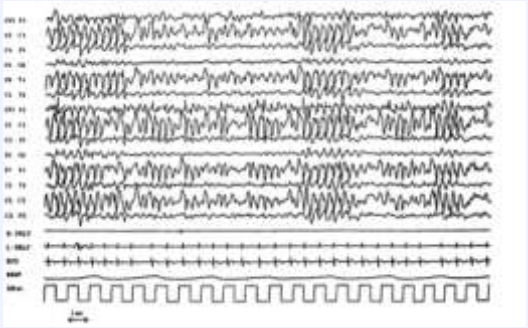
- **Drugs mentioned in more than 3 individual reports**

- Antidepressants +++
- Anticonvulsants (BZD, CBZ, LAM, LEV, VAL, VBG)
- Antibiotics
- Antipsychotics
- Cocaine
- Camphor +++
- Cephalosporins +++
- Cisplatin
- Cloroquine
- Ecstasy
- Isoframide
- Isoniazid +++
- Lithium
- Methotrexate
- N-acetylcysteine
- Tiagabine +++
- Tetramine
- Theophylline +++

(Ep res 2010 in press)

Drug or toxin induced NCSE - Tiagabine

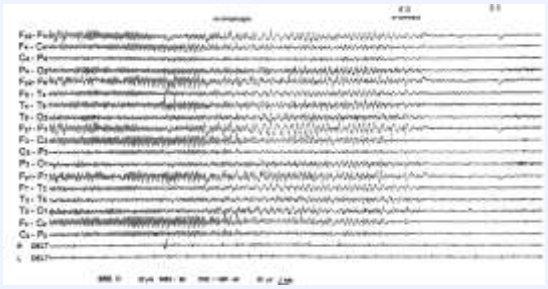
- Large list of drugs/toxins can cause seizures, and several typically cause a nonconvulsive confusional state. Common examples are tiagabine and IV contrast agents.
- TGB - FDA safety alert because of large numbers of cases
- At NHNN 7 (7.8%) of 90 TGB patients had electrographically confirmed NCSE over a 3 year period
  - Higher frequency than NCSE on other drugs
  - EEG shows prolonged runs of Spike/wave
  - 2/7 also had GTCSE
  - <6 months therapy in 6/7.
  - These cases were not toxic encephalopathy, although probably are
  - GABA-ergic effect ?

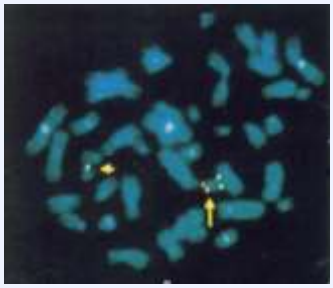


(Koepp et al Epilepsia 2005: 1625)

Uncommon causes of NCSE – chromosomal disorders

- Ring chromosome 20
  - Defined in 1976 (Borgaonkar et al)
  - Epilepsy, behavioural problems and mild learning disability
  - Seizures typically take the form of prolonged confusional states twilight states) with or without automatisms
  - EEG also shows rather characteristic long trains of theta, some without clinical abnormalities





(Canevini et al Epilepsia 1998: 942)

Uncommon causes of SE – autoimmune 'limbic encephalitis'

- **Autoimmune LE**
  - First case described by Brierley 1960
  - First case associated with serum antibodies - thyroid microsomal AB (Hashimotos encephalitis) 1966 (Brain)
  - Since 1980s, a variety of ABs found, some with tumours and some 'idiopathic'
  - Cell surface antibodies - B-cell - and easier to treat
  - Intracellular antibodies - T-cell - less responsive to therapy

Intracellular antibodies	Extracellular antibodies
Hu/ANNA-1	VGKA
Ms-2	NMDA-R
CRMP-5	Others (eg glycine, adenylate kinase 5, BR serine/threonine kinase)
Amphiphysin	
GAD	

Uncommon cause of SE - autoimmune limbic encephalitis

- **Clinical features**
  - Subacute encephalopathy with memory disturbance, behavioural/personality change/psychiatric disorder, and seizures (SE is common presenting symptom)
  - 'Limbic' in flavour, but often widespread cerebral symptoms and signs (depending on ABs involved)
  - Epilepsy often characteristic in form; often presents with SE.
  - Prognosis of epilepsy depends on underlying cause
- **Investigations**
  - MRI scanning often shows hippocampal high T2 signal
  - CSF often abnormal sometimes with oligoclonal bands
- **Frequency of malignancy**
  - Depends on ABs

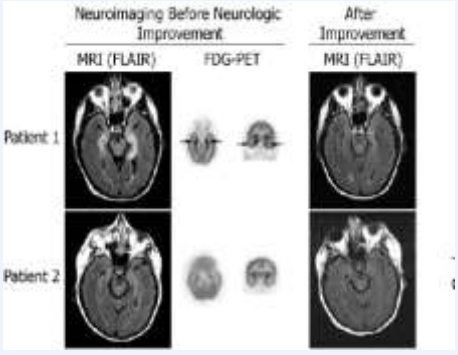
Uncommon causes of SE – autoimmune limbic encephalitis

- **Neoplastic autoimmune LE**
  - Neurological symptoms precede tumoural symptoms in 66%; LE associated with other signs
  - Anti Hu: small cell lung cancer
    10% have LE, others cerebellar, PN, autonomic
  - Ma-2: intratubal germ cell tumours of testes
    Other features include hypothalamic and brainstem signs
  - Amphyphysin: LE and 'stiff person syndrome
  - GAD: LE with 'stiff person syndrome'

- **Non-neoplastic autoimmune LE**
  - Voltage-gated potassium channel antibodies
  - NMDA-R antibodies First case described by Brierley 1960
  - Hashimotos encephalitis (STREAT)

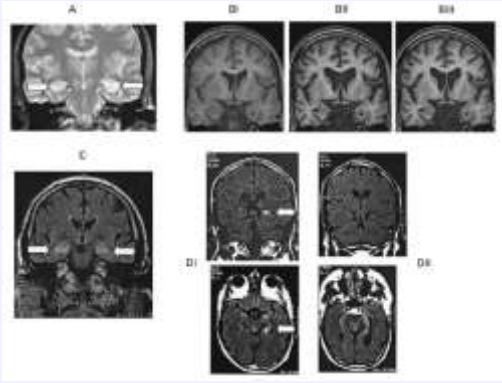
Uncommon causes of SE – 'Hashimoto's encephalitis'

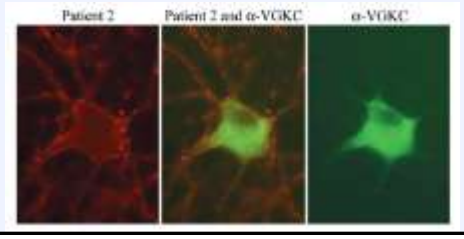
- **Hashimoto's encephalitis (STREAT) – illustrative case**
  - 65 yr old male – sudden onset SE followed by psychosis, szs, behavioural change, cerebellar and brain stem signs
  - High titres of thyroid microsomal ABs (others negative)
  - Rapid response to IVIg and steroids and now rituximab
  - 4 year follow-up - still requires immunotherapy but now virtually asymptomatic



LE with Voltage Gated potassium Channel antibodies

- First described in 2001
- Cause of LE, with other regions also involved
- < 30% only with tumours
- Overlap with Morvan's syndrome
- Response to immunotherapy
- Series of 10 cases (Buckley 2004) (44-79 yrs; 9 males)
  - Malignancy in 0/10
  - OCBs in CSF in 1/10
  - Neuromyotonia in 1/10
  - Response in immunotherapy in 6/10
- Similar cases without Abs
- More common than recognised
- Queen Square treatment regimen – steroids, IVIg or Pl exchange, azoth, rituximab

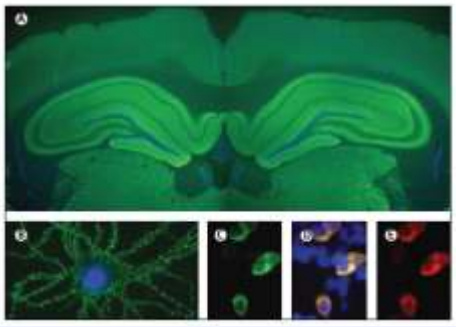




Uncommon causes of SE - LE due to NMDA-R antibodies

- First described in 2007 by Dalmau
- Severe but treatment responsive LE; 90% young women
- Present with rapid deterioration with psychosis, delusions, amnesia, szs, stupor/coma, stereotyped abnormal movements
- Paraneoplastic; although some cases without tumour (esp male)

- Case series of 100 cases (Dalmau 2008)
  - 59% tumours (commonest ovarian teratoma)
  - 75% recovered or mild deficit
  - 25% died
  - Main epitope is the extracellular N-terminal domain of NR1 subunit



Dalmau et al Lancet Neurol 2008: 1091)

Uncommon causes of SE - Mitochondrial Disease

- **Mitochondrial disease**
  - Defects in MtDNA → MELAS/MERFF/MNGIE etc
  - Mutation in nuclear genes that control mtDNA (eg *POLG1*)
- ***POLG1* mutations**
  - Mutations cause a spectrum of disease - Alpers disease, PEO, mitochondrial SCA, occipital lobe epilepsy

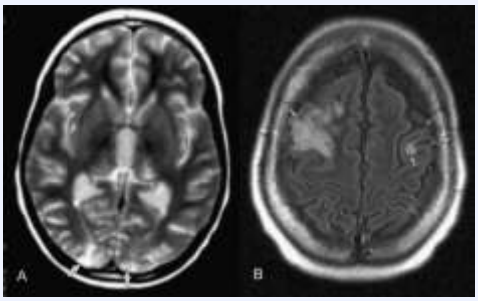
***POLG1* mutations → occipital lobe epilepsy (A467T and W748S)**
- Adult-onset (oldest 58yrs)
- Occipital lobe epilepsy
- All cases experience SE and usually intractable CPSE
- Death usually within 8 years

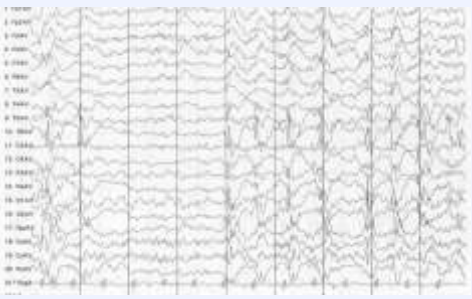
***POLG1* mutation → Alpers' disease**
- Subacute presentation, death within 12 months
- Occipital predominance
- EPC, CPSE, GTCSE invariable

POLG1 mutations causing Occipital lobe epilepsy

- First described in 2008
- Present with occipital lobe partial seizures
- As with other mitochondrial SE is common (CPSE, GTCSE, but no EPC)
- SE is often terminal event
- Valproate can precipitate hepatic failure

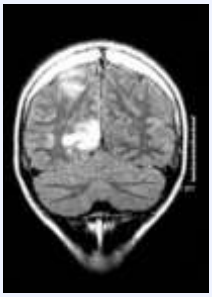
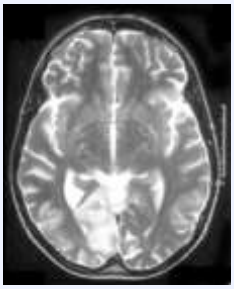
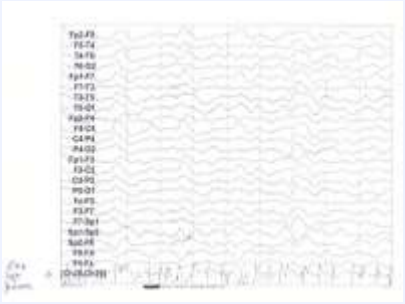
(Engelsen et al. Brain 2008 818)





Uncommon causes - *POLG1* mutation → Alpers' disease

- **Alpers' disease – Illustrative case**
  - 18 year old male – always thin
  - Subacute GI disturbance, with normal liver function
  - Laparotomy – duodenal obstruction
  - Post-op GTSE and subsequent EPC
  - MRI initially normal; CSF 8 cells; lactate normal
  - Progressive decline; brain biopsy; death in 6 months

Treatment of tonic-clonic SE: the importance of staging

Stage 1: Premonitory / early SE
(Usual treatment = benzodiazepine)

↓

Stage 2: Established SE
(Usual treatment = PTH or PB)

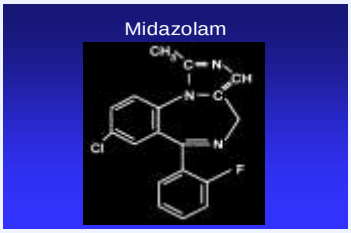
↓

Stage 3: Refractory SE
(Usual treatment = general anaesthesia)

- **Refractory TCSE is defined as 'The stage of SE reached when seizures have continued despite treatment for 60 minutes or more, and requiring general anaesthesia (Frequency – 2-5/100,000/yr)**

Out-of-hospital therapy

- **Buccal/intranasal administration of midazolam**
- **Midazolam**
  - **water soluble → rapid absorption**
  - **lipid soluble → rapid entry to brain**

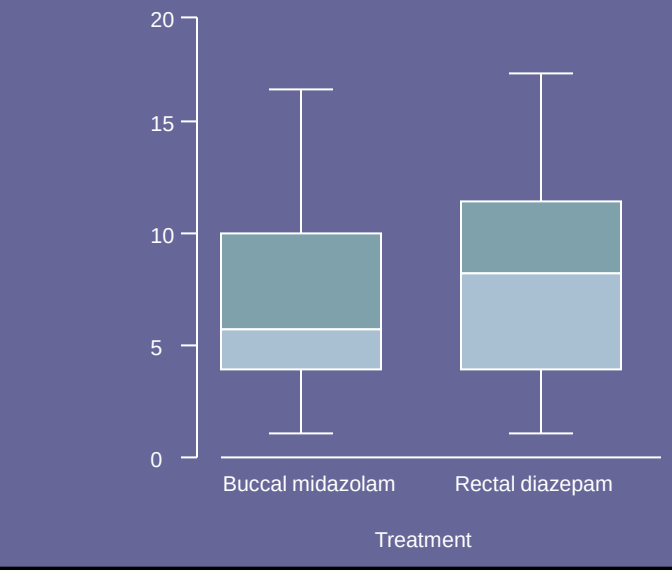


Out of hospital therapy - buccal midazolam .v. rectal diazepam in acute seizures

- **RCT in a residential school setting**
- **79 children with continuous seizures of >5mins**
- **Tonic clonic seizures: Midazolam 24/40**
  Diazepam 22/39
- **Midazolam 10mg in 2ml on buccal mucosa**
- **Diazepam 10mg via rectal tubule.**
- **Seizure control: Midazolam → 30/40 (75%)**
  Diazepam → 23/39 (53%)

(Scott; Lancet 1999 353: 623)

Time from drug administration to end of seizure (min)



RCT of buccal midazolam .v rectal diazepam in children

- **Multicentre RCT - buccal midazolam .v. rectal diazepam 0.5mg/kg (approx). 219 episodes.**
- **Acute seizures and SE presenting to A&E (mean 30-47 mins of seizures before trial; 31% had had prior initial therapy)**

Outcome	**MDZ (n= 109)**	**DZP (n=110)**
- Seizure control (within 10 mins)	**56%**	**27%**
- Time to seizure control (median)	**8 mins**	**15 mins**
- Required lorazepam	**33%**	**57%**
- Respiratory depression	**5%**	**6%**

- **Conclusion – buccal midazolam is more effective than rectal diazepam**
- **50% control of seizures >30 mins**

(McIntyre et al. Lancet 2005: 366: 205-

Stage 2 – established SE: post-BZD AED therapy

- **RCTs in established SE**
  - Diazepam/phenytoin vs phenobarbital - 2 RCTs (n=222)
  - Phenytoin vs phenobarbital - 1 RCT (n= 186)
  - Diazepam/phenytoin vs phenytoin - 1 RCT (n= 196)

- **Conclusions (4 RCTs):**
  1. No significant differences
  2. trend to favour DZP/PHT over PB
  3. trend to favour PB over PHT

Stage 2 – established SE

- **Licensed medications - phenytoin and phenobarbital**
  - Both carry risk of cardiovascular and cerebral depression
  - Both cause hypotension
  - Both are EIAEDs (and PB also self induction)
  - Both interact with other drugs
  - PTH carries cardiac risk and risk of infusion site damage
  - Both have poor pharmacokinetics

- **Unlicensed alternatives:**
  - Valproate at least 8 open case series (>200 pts) and one RCT (VPA vs PTH)
  - Levetiracetam at least 20 open case series (>150 patients)
  - Control rates equivalent historically to PHT/PB
  - No cardiovascular toxicity
  - No hypotension
  - No cardiac risk
  - No risk to infusion site
  - LEV has no enzyme induction nor drug interactions

Treatment of refractory stage of SE (>90mins): conventional protocol

- **Thiopentone 100-240 mg IV bolus over 20 secs then 50 mg boluses every 2-3 mins then IV infusion 3-5 mg/kg/hr to obtain burst suppression.**

or

- **Propofol 2 mg/kg IV bolus, repeated, then IV infusion of 5-10 mg/kg/hr to obtain burst suppression.**

or

- **Midazolam 0.1–0.3mg/kg IV bolus at a rate not exceeding 4mg/min, then IV infusion 0.05-0.4 mg/kg/hr to obtain burst suppression.**

Alternatives: Pentobarbitone, ketamine, etomidate, desflurane, isoflurane

Stage of refractory SE – which is the best general anaesthetic

	Midazolam	Barbiturate	Propofol
Short term mortality (7 series)	17-69%	20-55%	26-88%
Accumulation	+++	++++	0
Tolerance	++++	++	0
AED action	++++	++++	0
Elim half-life	6hr	24-36hr	1-2hr
Other problems			'infusion syndrome'

Stage of refractory SE – which is the best general anaesthetic

	Midazolam	Pentobarbital	Propofol
N. of patients	54	106	33
Failed sz control	20 %	8 %	27 %
Breakthrough szs	51 %	15 %	12 %
Withdrawal szs	63 %	43 %	46 %
Hypotension	30 %	77 %	42 %
Mortality	46 %	48 %	52 %

A "meta-analysis" (Classen et al 2002)

08KP0090 / May 2008

Reasons for failure of therapy to control SE

- Inadequate emergency antiepileptic drug therapy
- Failure to initiate maintenance antiepileptic drug therapy
- Hypoxia, hypotension, cardio-respiratory failure, metabolic disturbance
- Failure to identify or treat the underlying cause
- Other medical complications
- Misdiagnosis (pseudostatus)

08KP0090 / May 2008

UCL

3rd London Innsbruck Colloquium on Acute Seizures and Status Epilepticus

Oxford UK : 7th - 9th April 2011

For further information:

www.statusepilepticus2011.eu

s.shorvon@ion.ucl.ac.uk

eugen.trinka@uki.at