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

Epilepsy Society of Thailand
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- 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
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

<table>
<thead>
<tr>
<th></th>
<th>Rochester USA</th>
<th>Switzerland</th>
<th>Bologna Italy</th>
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<tbody>
<tr>
<td>Population</td>
<td>1,090,055</td>
<td>1,735,420</td>
<td>336,876</td>
</tr>
<tr>
<td>No. of cases</td>
<td>199</td>
<td>172</td>
<td>44</td>
</tr>
<tr>
<td>SE Incidence</td>
<td>18.3/100,000/yr</td>
<td>10.3/100,000/yr</td>
<td>13.1/100,000/yr</td>
</tr>
<tr>
<td>Prior epilepsy</td>
<td>44%</td>
<td>33%</td>
<td>39%</td>
</tr>
<tr>
<td>Acute sympt</td>
<td>50%</td>
<td>63%</td>
<td>34%</td>
</tr>
<tr>
<td>Remote sympt</td>
<td>20%</td>
<td>28%</td>
<td>34%</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>14%</td>
<td></td>
<td>7%</td>
</tr>
<tr>
<td>Other/NK</td>
<td><strong>16%</strong></td>
<td><strong>9%</strong></td>
<td><strong>25%</strong></td>
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</tbody>
</table>

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, isonaiizid)
- 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
  - Cloroquione
  - Ecstasy
  - Isoframide
  - Isoniaizid +++
  - Lithium
  - Methotrexate
  - N-acetyl cysteine
  - 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?  

(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
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

<table>
<thead>
<tr>
<th>Intracellular antibodies</th>
<th>Extracellular antibodies</th>
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<tbody>
<tr>
<td>Hu/ANNA-1</td>
<td>VGKA</td>
</tr>
<tr>
<td>Ms-2</td>
<td>NMDA-R</td>
</tr>
<tr>
<td>CRMP-5</td>
<td>Others (eg glycine, adenylate kinase 5, BR serine/threonine kinase)</td>
</tr>
<tr>
<td>Amphiphysin</td>
<td></td>
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<tr>
<td>GAD</td>
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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)

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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/MERRF/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)
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

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<tr>
<th></th>
<th>MDZ (n= 109)</th>
<th>DZP (n=110)</th>
</tr>
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<tbody>
<tr>
<td>Seizure control (within 10 mins)</td>
<td>56%</td>
<td>27%</td>
</tr>
<tr>
<td>Time to seizure control (median)</td>
<td>8 mins</td>
<td>15 mins</td>
</tr>
<tr>
<td>Required lorazepam</td>
<td>33%</td>
<td>57%</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>5%</td>
<td>6%</td>
</tr>
</tbody>
</table>

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

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 (>90 mins): 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 0.1–0.3 mg/kg IV bolus at a rate not exceeding 4 mg/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

<table>
<thead>
<tr>
<th></th>
<th>Midazolam</th>
<th>Barbiturate</th>
<th>Propofol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short term mortality (7 series)</td>
<td>17-69%</td>
<td>20-55%</td>
<td>26-88%</td>
</tr>
<tr>
<td>Accumulation</td>
<td>+++</td>
<td>++++</td>
<td>0</td>
</tr>
<tr>
<td>Tolerance</td>
<td>++++</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>AED action</td>
<td>++++</td>
<td>++++</td>
<td>0</td>
</tr>
<tr>
<td>Elim half-life</td>
<td>6hr</td>
<td>24-36hr</td>
<td>1-2hr</td>
</tr>
<tr>
<td>Other problems</td>
<td></td>
<td></td>
<td>‘infusion syndrome’</td>
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Stage of refractory SE – which is the best general anaesthetic

<table>
<thead>
<tr>
<th></th>
<th>Midazolam</th>
<th>Pentobarbital</th>
<th>Propofol</th>
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<tbody>
<tr>
<td>N. of patients</td>
<td>54</td>
<td>106</td>
<td>33</td>
</tr>
<tr>
<td>Failed sz control</td>
<td>20 %</td>
<td>8 %</td>
<td>27 %</td>
</tr>
<tr>
<td>Breakthrough szs</td>
<td>51 %</td>
<td>15 %</td>
<td>12 %</td>
</tr>
<tr>
<td>Withdrawal szs</td>
<td>63 %</td>
<td>43 %</td>
<td>46 %</td>
</tr>
<tr>
<td>Hypotension</td>
<td>30 %</td>
<td>77 %</td>
<td>42 %</td>
</tr>
<tr>
<td>Mortality</td>
<td>46 %</td>
<td>48 %</td>
<td>52 %</td>
</tr>
</tbody>
</table>

A “meta-analysis” (Classen et al 2002)

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)
3rd London Innsbruck Colloquium on Acute Seizures and Status Epilepticus
Oxford UK: 7th - 9th April 2011

For further information:
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