STATUS EPILEPTICUS: DIAGNOSIS AND PREHOSPITAL TREATMENT

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DISCLOSURE

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• Chair, Steering Committee, EPINOV (France)
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Learning Objectives

- Key aspects in the diagnosis of status epilepticus
- Consequences of misdiagnosis and delay in treatment of status epilepticus
- Evidence for effectiveness of pre-hospital treatment of status epilepticus
Key Messages

• Status Epilepticus is often missed in the community
• Longer duration of Status Epilepticus is associated with lower recovery and survival
• Pre-Hospital treatment is associated with better outcomes
  • Shortened duration, lower recurrence, fewer hospitalizations and ICU
• Effective Pre-hospital Medications include
  • Rectal Diazepam
  • Buccal or Intramuscular Midazolam
  • Intravenous Diazepam or Lorazepam
SOME NUMBERS

INCIDENCE (P/100,000)
- 25 Status Epilepticus
- 5 Refractory
- 3 Super R

5% - 17% Hospital Admissions with SE evolve to SRSE

35% - 43% Mortality

>50% Develop cognitive deficits

NUMBER OF DAYS
In THERAPEUTIC COMA = cognitive deficits

60% Of costs related to SE are due to SRSE

Strzelczyk, et al, Epilepsia 2017
**A condition resulting from failure of mechanisms responsible for seizure termination**

- **time point t1** = abnormally prolonged seizures
- **time point t2** = *Can have long-term consequences*: neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.

<table>
<thead>
<tr>
<th></th>
<th>GTC</th>
<th>Focal impaired unawareness</th>
<th>Absence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1 - start treating as status</strong></td>
<td>5 min</td>
<td>10 min</td>
<td>10-15 min</td>
</tr>
<tr>
<td><strong>T2 - treat more aggressively</strong></td>
<td>30 min</td>
<td>60 min</td>
<td>unknown</td>
</tr>
</tbody>
</table>
ILAE Classification of Status Epilepticus

4 Axes

1: Semiology
   - Convulsive
     - convulsive
     - myoclonic
     - focal
     - tonic
     - hyperkinetic
   - Non-convulsive
     - with coma
     - without coma
     - generalized
     - focal
     - unknown

2: Etiology
   - Known
     - acute
     - remote
     - progressive
     - syndromes
   - Unknown

3: EEG
   - Location
   - Pattern
   - Morphology
   - Time related
   - Modulation
   - Intervention

4: Age
   - Neonatal
   - Infancy
   - Childhood
   - Adolescence
   - Adulthood
   - Elderly

Trinka, Epilepsia 2015
Why is Pre-hospital Treatment of SE Important?

- Longer duration $\rightarrow$ brain damage and sequelae
- Longer Duration and etiology are the main determinants of outcome
- Longer duration $\rightarrow$ lower chance of responding to subsequent AEDs
- Pre-hospital treatment $\rightarrow$ Improves outcomes
The Excitotoxic Cascade

- Excessive Glutamate release
- Cellular Ca\(^{++}\) influx
- Free radical accumulation
- Neuronal reorganization and hyperexcitability
- Cell death
Prognostic Factors in Status Epilepticus

### Main Risk Factors for Mortality

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration &gt;1 hour</td>
<td>9.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Etiology: Anoxia</td>
<td>3.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Age</td>
<td>1.4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

### Duration important across etiologies

<table>
<thead>
<tr>
<th>Group</th>
<th>Good outcome</th>
<th>Poor outcome</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (min)</td>
<td>2.4</td>
<td>11.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AED W/D</td>
<td>1.7</td>
<td>4.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.5</td>
<td>4.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CNS Infection</td>
<td>1.7</td>
<td>18.5</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Lowenstein, Epilepsia 1999
Recognizing Status Epilepticus

150 patients with SE
Swiss Hospital 10 years

<table>
<thead>
<tr>
<th>Prehospital Diagnosis</th>
<th>SE Suspected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epileptic event</td>
<td>67</td>
</tr>
<tr>
<td>SE</td>
<td>32</td>
</tr>
<tr>
<td>Seizures</td>
<td>35</td>
</tr>
<tr>
<td>No epileptic event</td>
<td>83</td>
</tr>
<tr>
<td>Unknown type</td>
<td>37</td>
</tr>
<tr>
<td>Stroke</td>
<td>39</td>
</tr>
<tr>
<td>Cardiac event</td>
<td>4</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>3</td>
</tr>
</tbody>
</table>

All converted from Convulsive to Non-convulsive

Non-Convulsive
- Not missed, 45, 36%
- Missed, 79, 64%

Convulsive
- Not missed, 22, 85%
- Missed, 4, 15%

Semlack, Neurology 2017
3 things to remember:

1. CSE is recognized, but NCSE is frequently missed.
2. NCSE is missed with older age and no seizure history.
3. Missed NCSE $\rightarrow$ lack of treatment and no recovery to functional baseline.

### Associations (multivariate*)

<table>
<thead>
<tr>
<th>Missing SE</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age (each additional year)</td>
<td>1.06*</td>
</tr>
<tr>
<td>• No history of seizures</td>
<td>6.43*</td>
</tr>
<tr>
<td>• Fatal etiology</td>
<td>2.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not getting benzodiazepines</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age (each additional year)</td>
<td>1.05*</td>
</tr>
<tr>
<td>• Glasgow CS (each added point)</td>
<td>1.21*</td>
</tr>
<tr>
<td>• Missed SE diagnosis (20% vs 50%)</td>
<td>$p&lt;0.001$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No recovery to baseline</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Missed SE diagnosis</td>
<td>3.83*</td>
</tr>
<tr>
<td>• Status severity score</td>
<td>1.35*</td>
</tr>
</tbody>
</table>

84% accurate in predicting a Missed Diagnosis of SE

Semlack et al, Neurology 2017
AVOIDING MISSED DIAGNOSIS

ETIOLOGY?
Most important determinant of Mortality

EMS TRAINING?
might improve detection
What kind of training

EEG – PORTABLE?
Feasible, interpretation?

BENZOS IF ↓ LOC?
Risk of overtreatment, morbidity, unnecessary intubation, hospitalization

PSYCHOGENIC?
Challenging management, risk of overtreatment

FOCUS ON CSE?
Worse consequences of missing diagnosis than NCSE
15 studies on timing to treatment

• Time to treatment
  • Prehospital Median 35 min (22 to 70)
  • Hospital Median 8 min

• Prehospital treatment
  • 52% by EMS, 13% by Family
  • 67% by Family if history of CSE

• Later treatment
  • Longer seizures
  • Decreased response to Benzos
  • Increased in-hospital mortality

Gainza-Lein et al, Seizure 2018
Factors related to delays in Pre-hospital management

- 92 patients, CSE, Helsinki area
- Delays in management
  - Focal seizures → delay diagnosis, treatment, anesthesia
  - Non-tertiary care hospital

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Range min–max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset-to-initial-treatment</td>
<td>35 min</td>
<td>0 min–77 h 5 min</td>
</tr>
<tr>
<td>Onset-to-first-ED</td>
<td>2 h 2 min</td>
<td>0 min–58 h 29 min</td>
</tr>
<tr>
<td>Onset-to-tertiary-hospital</td>
<td>2 h 25 min</td>
<td>37 min–277 h 40 min</td>
</tr>
<tr>
<td>Onset-to-diagnosis</td>
<td>2 h 10 min</td>
<td>6 min–70 h 40 min</td>
</tr>
<tr>
<td>Onset-to-anesthesia</td>
<td>2 h 55 min</td>
<td>0 min–81 h 45 min</td>
</tr>
</tbody>
</table>

Kämppi et al, Neurocritical care 2015
Children and Adults with repetitive seizures

Rectal Diazepam vs Placebo

N=45
N=46

Rectal Diazepam
Rectal Placebo

Rectal diazepam administered at home by caregivers, is an effective and well tolerated treatment for acute repetitive seizures

Dreifuss et al, NEJM 1998

Median Dose
Children 20mg
Adults 37.5mg

Seizures per 1000 patient days

All patients (n=45)
Children (n=25)
Adults (n=20)
All patients (n=46)
Children (n=22)
Adults (n=24)
Benzodiazepines are safe and effective out-of-hospital. Lorazepam is likely to be a better therapy than diazepam.
Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

- 4314 paramedics in 79 receiving hospitals in USA
- Randomized, controlled, blinded, non-inferiority
- Excluded: trauma, hypoglycemia, cardiac arrest, bradycardia <40 per minute, allergy, pregnant

- BTC Seizure >5 minutes
- Randomization
  - 448 = 20 mg MDZ IM + IV placebo
  - 445 = 4 mg LZP IV + IM placebo

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>MDZ</th>
</tr>
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<tbody>
<tr>
<td>No. of subjects — %</td>
<td>258 (57.6)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>0.88 (0.79–0.98)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICU admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects — %</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
</tr>
</tbody>
</table>

IM Midazolam is at least as safe and effective as IV Lorazepam
Same study: Patients <18 years

Seizures controlled
- 68% MDZ vs 71% LZP

Welch et al, Epilepsia 2015
Pre-hospital midazolam for benzodiazepine-treated seizures before and after the Rapid Anticonvulsant Medication Prior to Arrival Trial: A national observational cohort study

- Observational cohort in United States --2010 through 2014
- Rates of midazolam use as first-line treatment over time
- 156,539 benzodiazepine-treated seizures
- Midazolam use increased from 26.1% in 2010 to 61.7% in 2014
- Rescue therapy and airway interventions declined over time

Stuhli-Leber et al, PLOSone 2017
Buccal Midazolam vs Rectal Diazepam in Children

• Buccal midazolam is at least as effective as rectal diazepam
• More socially acceptable and convenient
• Preferred treatment for outside hospital treatment

Scott et al, Lancet 1999