Seizures in Critical Care

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Critical Care Neurology

- Encephalopathy
- Brain death
- Increased intracranial pressure
- Neuromuscular crisis
- Seizures & Status epilepticus
  - Diagnosis
  - Investigation and Monitoring
  - Treatment and prophylaxis

Seizures in Critical Ill

- A common neurologic complication

- Critical illness (appropriate triggers)
  - Lower threshold for clinical and subclinical seizures
  - Protective factor (inhibitor) less effective
    - Paroxysmal excitation

- Subclinical seizures and status epilepticus
  - Common in ICU (10-20%)
  - False negative from a standard 30-minute EEG

Clinical spectrum of seizures in ICU

- Many types
  - Depending on the region of brain involved

- 2 types
  - Partial vs. generalized
    - Extent of cortical involvement
    - Distinct neuroanatomic mechanisms

Common presentation of seizures in ICU

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>Clinical expression</th>
</tr>
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<tbody>
<tr>
<td>Focal motor</td>
<td>Face or limb motor seizure, no alteration of sensorium</td>
</tr>
<tr>
<td>Complex partial</td>
<td>Disturbed sensorium, automatisms</td>
</tr>
<tr>
<td>Generalized tonic-clonic</td>
<td>Loss of consciousness, generalized convulsions</td>
</tr>
<tr>
<td>Nonconvulsive status</td>
<td>Disturbed sensorium or loss of consciousness without associated motor manifestations</td>
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</tbody>
</table>
Focal seizures

- Structural disease (Local excitatory aberrations)
  - A portion of the cortex and its corresponding functional systems
  - Spreading to adjacent cortical regions via local synaptic connections
- Simple partial seizures
  - Example: the classic "Jacksonian march"
- Complex partial seizures (esp. temporal epilepsies)
  - More involved: the recruitment of deeper brain elements
  - Affect conscious behavior: limbic brain, hippocampus or amygdala
  - Automatisms: ictal events, speech or behavioral mannerisms
  - Lip smacking, blinking, or repetitive hand movements
- Non-motor: more difficult to diagnose

Focal epileptic discharges and slow delta from left hemisphere

Generalized seizures

- Primary generalized
  - No cortical nidus identified
  - ? Focal but fast spreading
  - Initiation: brainstem/subcortical structure
  - Propagation: paroxysmal activity; via cortical networks or cortical-subcortical circuits
  - Bilateral symmetric/synchronous in clinical and EEG

Generalized tonic-clonic seizures

Etiologies

- Seizures as a consequence of critical illness
- Primary neurologic causes

Seizures as a consequence of critical illness
Etiology

- Sepsis
- Hemodynamic instability
- Hypoxia/ischemia
- Metabolic abnormalities (30-35%)
  - Hyponatremia
  - Hypoglycemia, hyperglycemia
  - Hypophosphatemia
  - Renal/hepatic dysfunction
  - Hypomagnesemia
- Drug/substance toxicity (15%-45%)
  - Antibiotics
  - Antidepressants
  - Antipsychotics
  - Bronchodilators
  - Local anesthetics
  - Immunosuppressive
  - Cocaine, amphetamines

Antibiotics

- Decrease central neuro-inhibitory tone
  - All antagonize the action of GABA
- Penicillin class:
  - Well established animal seizure model for focal epilepsy
  - Primary proconvulsant effect by blocking GABA Cl channels
  - Prevent GABA binding to GABA receptors → inhibiting Cl currents
  - Renal insufficiency: a predisposing factor for β-lactam drug toxicity

Carbapenem

- Imipenem/cilastatin
  - In rat, induce convulsive behavior at lower serum concentrations than other penicillins
  - A risk for seizures of 1.8% to 6.0%
  - More severe than other antibiotics
- Newer agents: meropenem, biapenem
  - lower convulsant risks than imipenem (risk 0.8%) as weaker affinity for the GABA-A receptor

Psychiatric medications

- Antidepressants
  - 0.1-4% risk of seizures, usually in an overdose
  - Low risk: trazodone, doxepin, monoamine oxidase inhibitors
  - Medium risk: tricyclics antidepressant, bupropion
  - Highest risk: maprotiline, amoxapine

- Psychotropic medication
  - Phenothiazines: lower seizure threshold: clinical & lab
  - Chlorpromazine: highest risk (3%-5%)

Theophylline

- Theophylline
  - Risk 8-14% in toxic dose (rare if level < 20 mg/mL)
  - Clinical can be notoriously difficult to treat
  - Mortality 50%
  - Rx: benzodiazipines, barbiturates, general anesthesia and hemodialysis
Anesthesia

- Lidocaine
  - Na+ channel antagonist
  - Topical, IV, intratracheal
  - Risk of seizures is well correlated with serum concentration as linearly dose-dependent
  - Low risk: at therapeutic levels (1–5 mg/L) for the treatment of arrhythmias and as an anesthetic supplement
  - High risk: level 8–12 mg/L.

Primary neurologic causes

Primary neurologic causes

Etiology

- Neurovascular: stroke, AVM, etc.
- Tumor: primary, metastatic
- CNS infection: abscess, meningitis, encephalitis
- Inflammatory disease: vasculitis, ADEM, limbic encephalitis
- Traumatic brain injury: contusion, hemorrhage
- Primary epilepsy

Primary neurologic causes

Stroke & seizures

- Incidence of seizures (4.4–11.8%)
- Most common cause of seizures in patient age> 60 years
- Location:
  - Lobar & subcortical > basal ganglia, thalamus
  - Posterior fossa (no risk)

Primary neurologic causes

Stroke & seizures

- Incidence
  - Higher seizures after monitoring with continuous-EEG (up to 22%)
    - 52% NCSE
    - 9% subtle
  - 1/3 minimal signs and all died

- Onset
  - Early (24 hours – 4 weeks): risk 1.8-15%
    - Excitatory or inhibitory alterations in the penumbral tissue
  - Late (>4 weeks): risk 2.5-15%
    - Result from gliosis and a meningoencephal scar
    - Almost 3 times higher risk for subsequent stroke → epilepsy
Stroke

- Ischemic stroke: risk 6% in non prophylaxis
- ICH: risk up to 28% (even prophylactic anticonvulsants)
- 2-3 times higher risk than ischemic stroke
- Status epilepticus
  - 1/4 - 1/6 of post stroke seizures
  - SE at stroke presentation: “less likely” to develop epilepsy
  - SE follow early or late seizures “likely” to develop epilepsy

Stroke

- Subarachnoid hemorrhage
  - Seizure may aggravate rebleeding (a serious concern)
  - 7% give prophylaxis AEDs until Pa aneurysms
  - Rebleeding also causes seizures
  - Continuous EEG monitoring
    - Detects NCS in 8% of patients who have SAH
    - Should monitor in unexplained coma or neurologic deterioration
  - Treatment
    - Coiling: lower risk of seizures (as less cortical injury) than clipping
      - A relative risk for seizures of 0.52

Stroke

- Cerebral venous sinus thrombosis
  - Seizure risk 29-50%
  - Early seizures (within 2 week from onset): risk 34-44%
  - Seizures predict
    - Motor or sensory deficits
    - Parenchymal lesion on admission (hemorrhage, infant, focal edema)
    - Presence of cortical vein thrombosis
  - Late seizures: risk 9.5%
  - Associated with early seizures

Stroke

- Reperfusion-hyperperfusion syndrome (RHS)
  - After carotid endarterectomy, carotid angioplasty and stenting or intracranial angioplasty
  - Early: immediately after the procedure
  - Later (7 hours – 12 days) average 7.6-12 day
  - Clinical
    - Postoperative headache, confusion
    - ICH, white matter vasogenic edema
    - Focal seizures

Head injury

- Risk of seizures: depending on severity of head injury & age
  - 3-12% in civilian
  - Up to 53% in military
- Time of onset (important)
  - Early (<1week)
    - 4.1% in moderate closed H.
    - 3.6% in severe H.
    - 50% occur in 24 hours
    - 25% occur in non-treated patients who have
      - 1 seizures immediately after int.
      - 2 depressed skull fracture
      - 3 KCS, 4 IDH
    - Independently associated with an unfavorable outcome
  - Late (>1week): risk of recurrence up to 90%
    - A greater predictor of significant long-term morbidity and poor outcome
    - Associated with early PTS, coma>1week, dural penetration, depressed skull fracture not surgically treated, and at least one nonreactive pupill


Brain tumor

• ICU patients with brain tumor
  • Seizure 35% of all tumor cases
    • Depends on pathology and location of the tumor
  • High-grade, rapidly progressive tumors
    • Glioblastoma, metastatic: risk 25-35%
  • Slow-growing tumors
    • Astrogloma, meningioma: risk 70%
    • Oligodendroglioma: risk 90%
  • Temporo-parietal regions with cortical gray involvement: highest incidence

High risk of seizures

Neuropathology and risk for seizures

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Risk</th>
<th>Higher risk</th>
</tr>
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<tbody>
<tr>
<td>Stroke</td>
<td>6%</td>
<td>12%</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td></td>
<td>Large cortical involvement</td>
</tr>
<tr>
<td>Intracranial tumor</td>
<td>&gt;25%</td>
<td>Cortical primary</td>
</tr>
<tr>
<td>Acute subdural (SDH)</td>
<td></td>
<td>Cortical contusion</td>
</tr>
<tr>
<td>Traumatic head injury</td>
<td>≥4%</td>
<td>Acute subdural (SDH)</td>
</tr>
<tr>
<td>Depressed skull fracture</td>
<td></td>
<td>Penetrating missile injury</td>
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<tr>
<td>Status epilepticus</td>
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<td>Evacuation/chronic SDH</td>
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Status epilepticus in ICU

• A rare admission diagnosis (0.2%)
• A complication of other medical illness (3.3%)
• A non-neurologic primary diagnoses
  • 12% incurred neurologic events in ICU
    • 28.3% seizures
      • Most common = status epilepticus
      • Most manifested as GTC (90%), then focal seizures
      • 5% complex partial = non-convulsive
      • 28.6% metabolic encephalopathy

General seizures

• Lasting for several seconds to 1-2 minutes
• Alterations in hemodynamic and respiratory indices
  • Tachycardia
  • High blood pressure
  • Desaturation
  • Excessive salivation
  • Depressed sensorium
• Postictal focal deficits (Todd paralysis)
  • Several hours: both focal and generalized seizures

Status epilepticus

• New definition: >5 minutes in length
• Complication of prolonged seizures
  • Precipitate systemic complications
  • Direct neuronal injury
• Mortality from SE 20-25%

Pathophysiology

- A reconfiguration of the excitatory and inhibitory network
- A breakdown of the Local inhibitory circuitry (GABA-mediated):
  - inhibitory surround → spreading
- Recurrent or prolonged seizures induced a positive feedback loop
  - “Seizures beget seizures”
  - The longer duration of SE the more difficult it is to terminate

Subtypes of status epilepticus

- 1) Generalized convulsive SE (GCSE)
  - Most common subtype in ICU
  - Overt convulsion → then in prolonged SE → Subtle
- 2) Non-convulsive status epilepticus
  - Awake, ambulatory or comatose
  - Complex partial status epilepticus
- 3) Focal SE (FMSE) or epilepsy partialis continua
  - Uncommon
  - Difficult to control
  - ? Unclear results in substantive injury to the cerebral cortex

Non-convulsive status epilepticus

- Used to be believed to be an uncommon SE subtype
- 5-10% of comatose patients examined by EEG
- Up to 34% of neurologic ICU patients
- Under detected due to inadequate monitoring

Periodic epileptiform discharges (PEDS)

Complication of prolonged GTCs

- Systemic
  - Acidosis
  - Hyperthermia
  - Rhabdomyolysis
  - Renal failure
  - Arrhythmias
  - Trauma
  - Pulmonary embolism
- Neurologic
  - Direct excitotoxic injury
  - Epileptogenic foci
  - Synaptic reorganization
  - Impaired protein synthesis

Consequences

- High excitatory amino acid–receptor activity
- Hippocampal complex, pyramidal cells of the cerebellum, amygdala, thalamus, and middle cortical lamina
- Permanent dysfunction in memory, balance, affect, and a general diminution in cognition
Prognosis of status epilepticus

- Poor prognosis
  - EEG: PLEDS
  - Seizures lasting > 1 hour (mortality odds ratio of 10)
  - Multiple seizure events
  - Convulsive SE with complications
    - Acidosis, hyperthermia, rhabdomyolysis
    - Aspiration and trauma

Investigation and Monitoring

Investigation

- Blood test & toxicology tests & septic work up (+/- CSF screen)
- CT, MRI brain
- Surface routine EEG recording
- Continuous EEG monitoring
  - ? Should perform in all ICU patients
  - ? Impact on clinical decision-making and outcome
  - +/- SPECT or PET(+/- depth electrode)

Monitoring

- Scalp EEG (the diagnostic test of choice)
  - For establishing the diagnosis of SE
  - Document a possible epileptic focus
  - For monitoring of the therapeutic response
    - Convulsive SE → NCSE 14%
    - Comatose 12 hours after initiate therapy for CSE:
      - Success Rx: comatose 87%
      - NCSE: comatose 100%
  - To prove pseudo-seizures

Role of continuous-EEG in ICU

- Generalized convulsive SE
  - To detect residual electrographic seizures (almost 50%)
  - 10% to 20% turning to NCSE
  - Unless a seizure fully resolves and the patient returns to an alert, cognitive baseline, an EEG should be obtained to exclude ongoing ictal activity

- Nonconvulsive
  - Esp. alteration of consciousness

- Equipment is not available in many hospitals

EEG in non-convulsive status epilepticus

- Primary
  - 1) Repetitive generalized or focal spike, sharp waves, spike-and-wave, or sharp-and-slow complexes at > 3/sec
  - 2) As above but <3 sec, but also meeting criteria 4 (below)
  - 3) Sequential rhythmic waves along with secondary criteria 1,2,3 +/- 4

- Secondary
  - 1) Incrementing onset: increase in voltage and/or increase/decrease in frequency
  - 2) Decrementing offset: decrease in voltage or frequency
  - 3) Postdischarge slowing or voltage attenuation
  - 4) Significant improvement in clinical state or EEG with anticonvulsant therapy
Compared overnight EEG vs. first routine 30-minutes

- Overnight EEG detected
- Overall
  - New or additional epileptiform abnormalities by 14%
  - Clinical and/or electrographic seizures 6%
  - Change in treatment 8%
  - Improvement attributed to change in treatment 4%
- In known cases with epilepsy
  - Treatment change with improvement 46%
- Seizures did not obviously affect outcome

Controversial in EEG

- Periodic lateralizing epileptic discharges
  - PLEDS if unilateral
  - BIPLEDS if bilateral/independent
  - PEDS if bilateral/uniform
  - Triphasic waves
- An interictal vs. ictal event
  - BIPLEDS (mortality of 61%) vs. PLEDS (29%)

Status epileptics severity scale (STESS)

- Reliably identifies SE patients who will survive
- Total score 0-6, <3 = good outcome

1) Age
   - <65 years = 0 pt, ≥65 years = 2 pts

2) Seizure type
   - Simple-partial, complex-partial, absence, and myoclonic in the context of idiopathic/genetic epilepsy = 0 pt
   - Generalized-convulsive = 1 pt, Nonconvulsive SE in coma = 2 pts

3) Level of consciousness
   - Alert, somnolent or confused = 0 pt, Stuporous or coma-tose = 1 pt

4) History of previous seizures
   - Yes = 0 pt, No = 1 pt

Status epilepticus: initial measures

- ABC & order EEG in the mean time
- CBG, thiamine, glucose
- Immediate IV BZD in 5 minutes
  - Lorazepam 5-10 mg, diazepam 20-40 mg, midazolam 5-20 mg
- PHT:
  - Loading 20 mg/kg, rate 50mg/min (goal level 15-20 mg/dL)
  - Additional 5-10 mg/kg if required (goal 30-35 mg/dL)
- VPA 20-50 mg/Kg
- Keppra, lecozamide, topiramate, etc
Initial drug for status epilepticus

Second-line agents

Refractory status epilepticus

- Rapid pharmacologic burst suppression/coma
  - Propofol 2 mg/kg then 150-200 mcg/kg/min infusion
  - Thiopental 4 mg/kg then 0.3-0.4 mg/kg/min
  - Midazolam 0.2 mg/kg, then 0.1-0.2 mg/hour
  - Pentobarbital 5-10mg/kg then 1-10 mg/Kg/h
- EEG monitoring
- Hemodynamic support

Status epilepticus: Bilateral periodic epileptiform discharges

Weaning from EEG seizure suppression

- Using c-EEG
- Burst suppression 12-48 hour before attempt to withdraw drug coma
- Adequate AEDs levels for chronic seizures control
- If seizure recur, re-bolus of 30-70% of original bolus
- Measure AEDs level

<table>
<thead>
<tr>
<th>First-line agents</th>
<th>Elimination time (time = 1/2 hour)</th>
<th>Recommended dosage range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepem</td>
<td>15</td>
<td>0.05-0.1 mg/kg</td>
</tr>
<tr>
<td>Midazolam</td>
<td>2-4</td>
<td>0.05-0.2 mg/kg</td>
</tr>
<tr>
<td>Dextropam</td>
<td>20</td>
<td>0.1-0.4 mg/kg</td>
</tr>
</tbody>
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<thead>
<tr>
<th>Second-line intravenous anticonvulsant</th>
<th>Dosage</th>
<th>Target serum level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin (PHT)</td>
<td>15-20 mg/kg</td>
<td>15-20 mcg/mL</td>
</tr>
<tr>
<td>Phenytoin (PMT)</td>
<td>15-20 mg/kg PE</td>
<td>15-20 mcg/mL</td>
</tr>
<tr>
<td>Valproate (VPA)</td>
<td>15-20 mg/kg</td>
<td>50-100 mcg/mL</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1000-1500 mcg q24h</td>
<td>7-10 mcg/mL</td>
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Abbreviation: PE, phenytoin equivalents.
Treatment of seizures in ICU

Generalized convulsive SE
- A strong consensus in aggressive treatment

Non-convulsive SE (NCSE)
- Debate
  - Benign, if in patients non-cerebral lesion, no permanent morbidity
  - More common following an anoxic-ischemic event or trauma
- Most epileptologists would agree that in such scenarios the presence of continuous paroxysmal activity may accentuate injury incurred by the primary insult

Seizure prophylaxis in the ICU

Medical illnesses or direct cerebral injury
- Predisposed to seizures

Medical illness
- Lower risk of seizures

CNS lesion
- Higher risk of recurrence
- Prophylactic treatment
  - Not a guarantee the outcome
  - ? Risk for toxicity

Stroke and prophylaxis

Controversial for AEDs prophylaxis

Ischemic or hemorrhagic stroke with a large cortical involvement or causing an acute confusional state in the early aftermath of a stroke were independent predictors of future seizures

The current ICH guidelines suggest antiepileptic treatment for 1 month in patients presenting with seizures

Stroke and prophylaxis

Alcoholic patients with ICH (x3 times risk for SE)
- Should be treated with GABAergic AEDs

Late seizures occur (after 2 weeks from onset)
- Long-term anticonvulsants as greater risk for epilepsy
- SAH: controversial

Brain tumor

Controversial for prophylaxis

Anticonvulsants may
- Interfere with corticosteroids, chemotherapy, and radiation treatment
- Induce more frequent and serious allergic reactions

Malignant glioma
- May prescribe
- Even adequate anticonvulsant therapy, seizures may occur
- The AAN practice parameters “do not” support prophylactic anticonvulsants in patients who have newly diagnosed brain tumors

Head injury

Severe head injury (Cortical injury)
- Strong data to support that prophylactic use of AEDs
- Cerebral contusion, acute subdural hemorrhage, depressed skull fracture, penetrating missile injury
- The current practice parameters by the AAN and the Brain Trauma Foundation advocate prophylactic treatment with “phenytoin” only during “the first 7 days” from head injury
Intracranial surgery

- The incidence of postoperative epilepsy
  - 17% after supratentorial intracranial surgery
  - Depends on pathology, location, type of surgical approach, presence of postoperative deficit, and a previous history of epilepsy
- A meta-analysis study: reviewing 30 publications
  - AEDS prophylaxis reduce the incidence of seizures
  - Postoperatively, patients without seizure: “taper off” AEDs

Summary

- Seizures in the ICU are more difficult to prevent, diagnose, and treat effectively
- Treatment of seizures and SE in an ICU is challenging
- The treatment of seizures requires a careful evaluation of toxic risk versus benefit and proper drug selection
- AEDs prophylaxis is still debated

Thank You