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STATUS EPILEPTICUS:

ASPECTS OF EMERGENCY CRITICAL CARE

Objectives and Goals

- Review current concepts, epidemiology, and pathophysiology of major motor SE (adults)
- Aspects important to critical care
- Diagnostic and treatment algorithms based on potential etiology and patient condition
- ED disposition of patients with SE
- Goal is to help improve care and outcomes

Disclosure and Support

- NETT (NIH-NINDS)
- RAMPART (NIH-NINDS)
- ALIAS 2 (NIH-NINDS)
- Currently, no industry funded support but will be involved with evaluation of biomarkers of brain injury (DOD and industry) and a brain injury clinical trial (DOD and industry)

What is Status Epilepticus?

- Continuous seizure or not regaining consciousness between seizures:
 - 30 minutes – Epilepsy Foundation of America
 - 10 – 20 minutes – Veteran’s Affairs SE Cooperation Study
 - **5 minutes** – newest definition (proposed 1999) not universally accepted
- Symptom of underlying disease or problem!!!

Proposed Definitions

- **Early or Impending SE** – continuous or intermittent seizure lasting more than 5 min. without full recovery in between
- **Established SE** – lasting > 30 min. without recovery
- Probably is really a continuum (more on this later)

Why the Confusion/New Definition?

- 40% of seizures lasting 10-29 min. stop spontaneously (mortality - 2.6%)
- Seizures > 30 min. mortality is 19%
- Mean duration of generalized seizure is 52.9 to 62.2 seconds (motor) and 59.9 sec. (EEG)
 - No seizure lasted > 2 min.
 - 5 minutes is > - 18 standard deviations
- No good reason to defer treatment if seizing 5 min.

Other Considerations

- **Subtle Status Epilepticus**
 - Usually with prolonged status
 - Motor and EEG manifestations can be less florid
 - Still requires aggressive therapy
- **Partially Treated Status**
 - Overt clinical signs stop
 - Subtle symptoms
 - EEG still shows seizure
 - About 10% of treated cases

Non-Convulsive SE

- Personality changes, lethargy, agitation, confusion, blinking, automatism, etc.
- Up to 13% of neuro ICU patients
- 16% severe head trauma
- In one study of continuous EEG monitoring (570 patients) – 92% (101) of 110 with seizures had non-convulsive seizures
- Difficult to Diagnose!!!

Myoclonic Status

- Usually post anoxia
- Extremely poor prognosis
- Often not treated as aggressively

Literature Applicability

- Studies are inpatients and outpatients
- Inpatient SE (by new definition) probably worse outcomes than those in ED only
- Data from NHAMCS

EPIDEMIOLOGY

- Richmond, VA study: 41 per 100,000/year
 - Overall mortality 22%
 - 27 per 100,000/year if young (15 – 59 years)
 - Mortality 14%
 - 86 per 100,000/year for elderly (\geq 60 years)
 - Mortality 38%
- “These numbers show that available treatments for SE are not effective enough...”

Delorenzo, et al. Neurology 1996

EPIDEMIOLOGY (cont.)

- NEJM Review
 - In U.S. 102,000 to 152,000 cases/year
 - 42,000 to 55,000 deaths (30% - 50% mortality???)
- Other Data
 - Swiss - 10.3/100,000/year
 - Germany – 17.1/100,000/yr
 - Rochester, MN – 18.1/100,000/yr
- Average – 20 episodes /100,000/year for Caucasians

ETIOLOGIES - Adults

- Low blood concentrations of AEDs (34%)
- "Remote Symptomatic Causes" (i.e. old neurological problems - 24%)
- CVA (22%)
- Anoxia/hypoxia (~13%)
- Metabolic abnormalities (~15%)
- Alcohol and drug related (~13%)

ETIOLOGIES - Pediatrics

- Fever (52%)
- "Remote symptomatic" (39%)
- Low AED levels (21%)
- Other (< 10%)

Outcomes

- Mortality for adults ~ 20% (from NEJM review that quotes a 1994 textbook - seems high for my population and for new definition)
- Those with first episode of SE are at future risk for SE and chronic epilepsy
- **PREDOMINANT FACTOR ASSOCIATED WITH OUTCOME IS CAUSE (age)**

Outcomes

- Based on etiology:
 - Low mortality – hx epilepsy with precipitating factors (low AED levels, sleep deprivation)
 - High mortality – anoxia, multiple medical problems
- Age (elderly)
- Prolonged or refractory
- Remember two above often associated with other issues!!!

Breaking SE

- Acute processes often difficult to treat
 - Electrolyte abnormalities (i.e. hyponatremia)
 - Renal failure
 - Infections (CNS or sepsis)
 - Acute stroke or head trauma
 - Other
- Chronic or established process often easier to break
 - Chronic seizures
 - Known chronic CNS disease
 - Alcohol withdrawal

Minimal Discussion of Requisite
“Physiology” and “Cell” and
“Molecular” Stuff

Changes in Physiology

- Fever
 - Look for other causes
 - Correlates with severity of cerebral injury
- Cardiovascular
 - Elevated BP (later can fall)
 - Tachycardia and cardiac arrhythmia
 - Elevated Pulmonary Artery pressures
- Blood and Fluids
 - Acidosis, hyperkalemia, CK, leukocytosis, etc
 - Abnormal CSF (WBC, protein)

Basic Mechanism of SE

- Appears that SE can become self-sustaining
 - Animal models (chemical or electrical) of SE
 - Human observations (no real "proof")
- Initiation of SE can be stopped by drugs that increase inhibition or reduce excitation
- Self-sustaining SE:
 - Easily stopped only by drugs that directly or indirectly inhibit glutamatergic neurotransmission
 - GABAergic and barbituates loose potency

Self-Sustaining SE

- Seconds to minutes
 - Existing GABA receptors move from synaptic membrane to endosomes
 - NMDA receptors move from storage to synaptic membranes
- Minutes to hours
 - Increase in proconvulsive neuropeptides
 - Depletion of inhibitory neuropeptides
- Hours to days
 - Change in gene expression
 - Neuronal death

Neuronal Cell Death

- This is what we want to prevent – “Time is brain”
- Can occur even in the absence of convulsive activity (animal and experimental models)
- Anecdotal in humans but probably occurs

Neuronal Loss After SE

- 1970's pointed to cerebral ischemia as the cause (loss in temporal lobe, Cortex, and particularly Hippocampus)
- Later models suggested enhanced neuronal activity (“excitotoxicity”)
 - Increased blood flow in rodent model more than compensated for increased cell activity
 - Calcium accumulation in mitochondria following prolonged NMDA receptor activity
 - altered mitochondrial function
 - necrotic or apoptotic cell death
 - supported by the neuro-protective effect of NMDA receptor antagonists

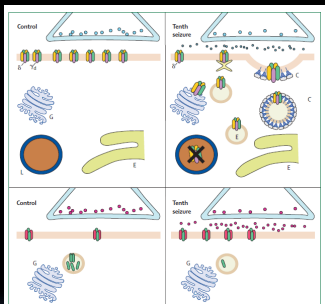


Figure 1. Model of one hypothesis of receptor trafficking in transition of single seizures to status epilepticus. Top: after repeated seizures, the synaptic membrane of GABA_A receptors forms clathrin-coated pits, which internalize as clathrin-coated vesicles (C), inserting the receptors because they are no longer within reach of the membrane. These vesicles develop into endosomes (E), which can deliver the receptors to lysosomes (L) where they are destroyed, or to the Golgi apparatus (G) from where they are recycled to the membrane. Bottom: by contrast, in NMDA synapses, subunits are mobilized to the synaptic membrane and assemble into additional receptors. As a result of this trafficking, the number of functional NMDA receptors per synapse increases whereas the number of functional GABA_A receptors decreases.

Chen JWY, Wasterlain CG, Lancet Neurol. 2006; 5:246-256

Pharmacoresistance

- Time-dependant resistance to benzodiazepines and others well documented in animal models
- In humans – early treatment more effective implying resistance is one possible explanation

Special Conditions in Critically Ill Patients

- More Difficult to treat
- Diagnosis can be difficult (sedation/paralysis)
- Causes different based on conditions:
 - Infections/sepsis
 - Liver Failure
 - Renal Disease
 - Transplant Patients
 - Metabolic Encephalopathy
 - Antibiotics

Need for ICU Care

- In S.F. 55% of ED patients were admitted to ICU
 - Complications of SE (i.e. respiratory insufficiency)
 - Treat the underlying cause of SE
- University of Virginia
 - Most common reason for ICU was need for mechanical ventilation and weaning after successful termination
 - This was a change (over a 15 year period) from the need to terminate SE
 - Use of lorazepam, faster therapy, airway skill in ED

Liver Failure

- Incidence 2% - 33% have seizures
- Pathophysiology
 - Ammonia
 - Toxins
 - Other associated abnormalities (sodium, etc)
- Pharmacokinetics
 - Albumin (Phenytoin and Valproic Acid)
 - Metabolism (poor liver clearance)
 - Consider using non-protein bound renal clearance meds for long-term therapy

Renal Disease

- 2% - 10% have seizures
 - Uremia
 - Metabolic disorders
 - Dysequilibrium from dialysis
- Protein-bound drugs not effectively dialyzed
- Renal metabolism (gabapentin, pregabalin, ethosuxamide, levetiracetam, phenobarbital, topiramate)
 - Serum concentrations decreased by 50%
 - Require replacement after dialysis

Organ Transplant

- Liver (25% - 30%)
 - Immunosuppressant agent toxicity (most commonly cited)
 - Cyclosporin
 - Tacrolimus
 - Metabolic abnormalities
 - Infections
 - Usually post-op day 4 - 6 (Benzo withdrawal ???)
 - Treatment usually phenytoin (short-term)
- Kidney (1% - 5%)
- Heart (2% - 6.5%)
- Lung (22% - 27%)
- Pancreas (13%)

Now What TO Do!

Evaluation

- ABCs
- Quick physical exam (primary survey)
- “Treat before diagnose”
- Begin thinking about root cause
- History ASAP
- RE-EVALUATE (secondary survey)!!!

“Time is Brain” Treatment Principles

- Time dependant loss of GABA receptors means decreasing responsiveness to benzodiazepines
- Tight timetable for treatment protocols
 - One treatment fails proceed to next (conventional)
 - Compressed algorithm (Silbergleit)
- Diagnostic strategy is important but should not delay treatment

Diagnostic Studies

- Because of new definition diagnostic workup needs are variable:
 - Little as H & P, glucose, and anticonvulsant levels
 - May be as much as a “jumbo” work-up
 - Multiple labs
 - CT or MRI
 - LP
- Re-evaluate!

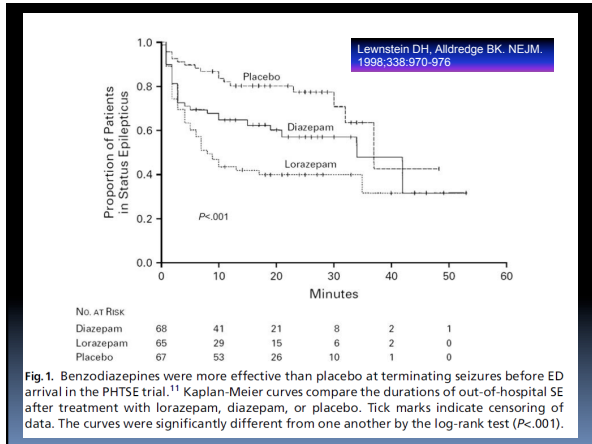
Treatment and Protocols

- ✓ Pre-hospital
- ✓ Traditional vs. proposed “accelerated” protocols (new thoughts)
- ✓ At DRH (and many other institutions) many have used the new the proposed “accelerated” protocol for years

Pre-Hospital Tx

- PHTSE trial showed that pre-hospital treatment is effective
 - Seizure > 5 minutes
 - Randomized placebo controlled
 - Lorazepam
 - Diazepam
 - Placebo
- Outcome
 - Mortality 30% (placebo) vs. 23% (Tx, not sig)
 - ICU admissions lower if stopped seizing by ED arrival (32%) than if still seizing (73%; $p < 0.001$)

Lewinstein DH, Alldredge BK. NEJM. 1998;338:970-976



What Else Does This Mean

- The “Time” is pre-hospital – Patients were “censored if:
 - Arrived in the ED and still seizing
 - Given “open-label” (standard?) therapy
- Some patients are in the field a long time and do not receive treatment
- Lorazepam is heat labile
- We need easier to give effective therapies

Potential EMS Practices

- IV Diazepam
- Rectal Diazepam
- IM Midazolam (not FDA approved but may be used by up to 30% of ambulances)
- RAMPART
 - RCT
 - IV lorazepam vs IM midazolam in pre-hospital setting

Treatment Protocols

