

CKD and Epilepsy



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Case Vignette

- 47-year-old man with ESRD on HD
- Missed 3 sessions of dialysis due to concerns for COVID-19 precautions
- ER with confusion, lethargy
- Exam: Altered mental status, lethargic, nystagmus, asterixis
- Labs: BUN: 75, Creatinine: 6.2

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Generalized Triphasic Waves



- Broad-based waveforms with three phases
- Bilaterally Synchronous
- 1-2 Hz
- Anterior to Posterior Time Lag

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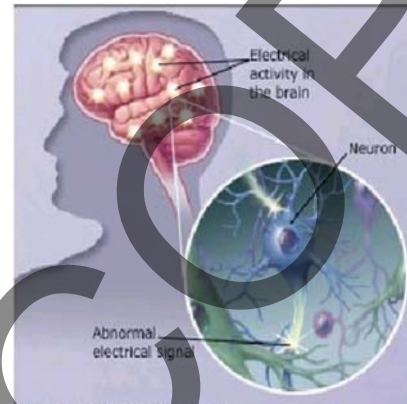
Course in Hospital

- Intubated for airway protection
- Intermittent eyelid twitches and body jerks
- Remained encephalopathic

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Seizures

- Sudden surge of electrical activity in the brain
- Usually self limited
- Not a disease by itself but symptom of many different disorders
- 10% of world population will have a seizure within their lifetime
- 1% will develop epilepsy



Provoked or Acute Symptomatic Seizure

- Seizure in an otherwise normal brain
 - Alcohol, barbiturate, benzodiazepine withdrawal
 - Metabolic derangements: hyponatremia, hypoglycemia, acute uremia
 - Fever, Sepsis
 - Drugs of abuse
- Incidence of seizure in chronic CKD: 10%
 - Decreased seizure threshold in an otherwise normal brain
 - 1/3 of patients with uremic encephalopathy develop seizures

Epilepsy

- From Greek: “To be seized by forces from without”
- **Epilepsy:** A chronic neurological condition characterized by recurrent epileptic seizures



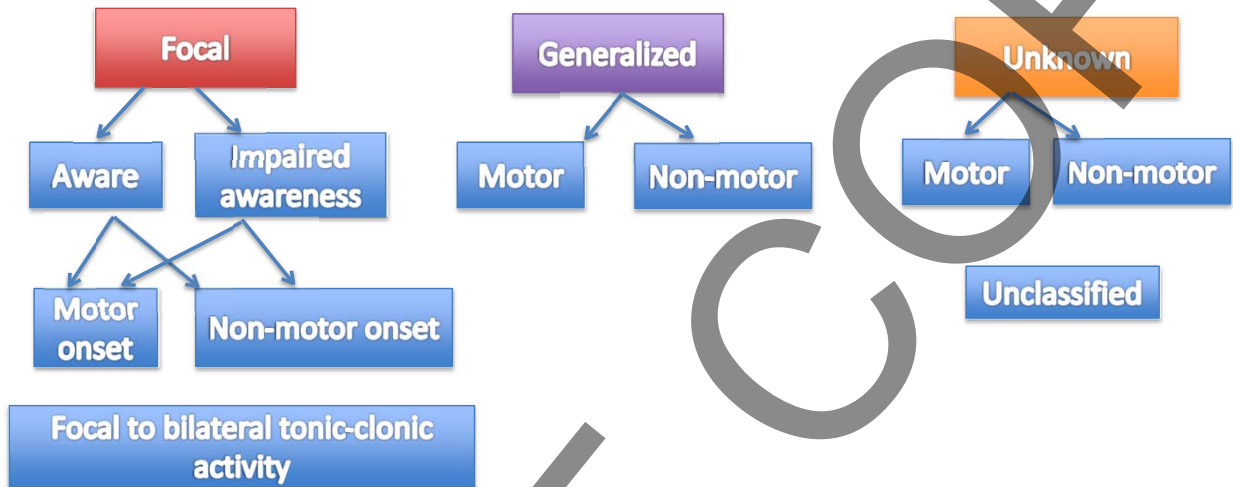
Epilepsy

- Third most common disorder of brain function
 - Following stroke and Dementia
- Epilepsy affects 2.5 million Americans of all ages
 - 315,000 children ≤ 14 years have epilepsy
 - 600,000 persons ≥ 65 years have epilepsy
 - 70% of new cases, no apparent cause



Seizure Classification

ILAE 2017 Basic Classification of Seizure Types



CKD and Seizures

- Two Major Categories:
 - Patients who develop provoked seizures in the setting of CKD
 - Patients with Epilepsy who develop CKD
- The incidence of seizures with chronic kidney failure is about 10%



Uremic Seizures

- Myoclonic seizures
 - Sudden involuntary jerky movements resulting from brief bursts of muscle activity
- Focal aware
- Focal motor with impaired awareness
- Absence seizures
- Generalized Tonic-Clonic
- Convulsive or non-convulsive status epilepticus
- In patients with acute persistent uremic encephalopathy, one should maintain a low clinical threshold for bedside EEG or continuous video-EEG and neurologic consultation



Causes of Seizures in Uremia



- Rapid accumulation of uremic toxins/Creatinine metabolites (Guanidino compounds)
 - GABA inhibition/ NMDA excitation
 - Enhanced cortical excitability (seizures)
- Electrolyte disturbances
 - Dysglycemia, hyponatremia, hypernatremia, hypomagnesemia, hypocalcemia, and acid-base disturbances
 - Secondary hyperparathyroidism (increase calcium in cerebral cortex)
- Dialysis Disequilibrium Syndrome
 - Reverse urea hypothesis
 - More rapid clearance of urea from plasma compared to the brain
- Air embolism
- Posterior Reversible Encephalopathy (PRES)

PRES Syndrome

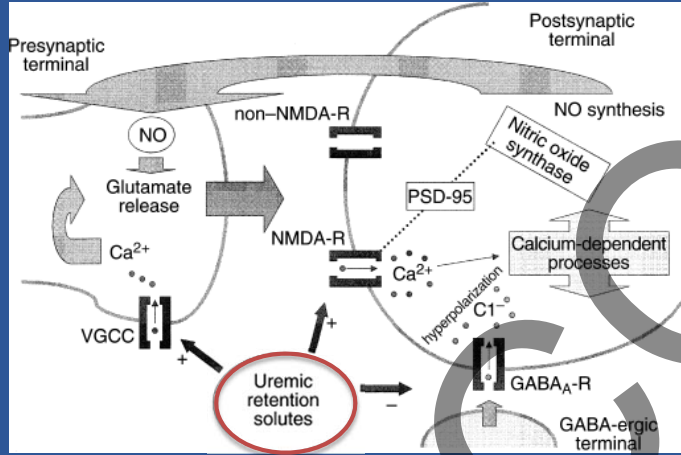
- Headaches, confusion, seizures and visual loss
 - Due to uncontrolled hypertension
 - Poor adherence to diet/ Excessive fluid intake
 - Acute glomerulonephritis or kidney failure
 - Hemolytic-uremic syndrome (HUS)
 - Medications that suppress the function of the immune system in kidney transplant patients (e.g. cyclosporine, Tacrolimus)
- PRES is accompanied by seizures in 60% to 75% of patients
 - Due to failure of vascular autoregulation that results in extravasation and vasogenic edema in the posterior cerebral circulation



Other Causes of Seizures in CKD

- Sepsis
 - Disruption and increased permeability of the BBB
- Antibiotics to treat sepsis
 - Penicillins, Cephalosporins (particularly Cefepime), Carbapenems, and Quinolones
- Higher incidence of stroke
- Subdural hematomas
 - Coagulopathy during HD, uremic platelet dysfunction, decreased subdural cavity pressure
- Management:
 - Reverse pathogenic process
 - If high risk for seizure recurrence treat with AEDs

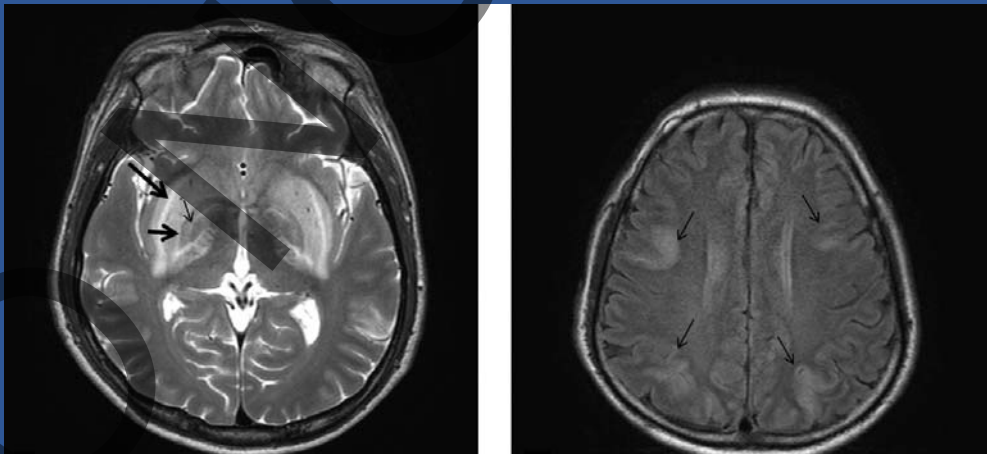
Excitatory and neurotoxic action of uremic retention solutes on the CNS



Kidney International 2003 63S25-S28DOI: (10.1046/j.1523-1755.63.s84.9.x)

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Patient Presenting with Uremia and Seizures: Lentiform Fork Sign



Neuroradiol J. 2014 Jun; 27(3): 288–292.
Clin Neurol Neurosurg. 2010 Nov;112(9):805-12.

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Kidney International
Volume 96, Issue 5, November 2019, Pages 1176-1184

Clinical Investigation

Epilepsy and antiseizure medications increase all-cause mortality in dialysis patients in the United States

Sa lina P. Waddy¹, Julia B. Ward², Adan Z. Becerra², Timothy Powers², Chyng-Wen Fwu², Konyal L. Williams³, Paul W. Eggers⁴, Kevin C. Albott⁴, Paul L. Kimmel⁴, P. B. J.

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Epilepsy and anti-seizure medications increase all-cause mortality in dialysis patients in the United States.

METHODS

USRDS N=148,294 patients with Medicare part A, B, and D

Hemodialysis or peritoneal dialysis

With and without epilepsy/seizures

Anti-seizure medications

Exposure

- No Epilepsy/Seizures 89%
- Epilepsy 9%
- Seizures 2%

Outcomes

Epilepsy associated with

- 15% risk of death Without neurology consultation
- 7% risk of death With neurology consultation
- 11% increased risk overall

CONCLUSION:
Epilepsy was associated with 1.11 times the risk of death and this relationship was modified by neurology consultation. Prescription of gabapentin among those with epilepsy diagnosis was associated with 1.08 times the risk of death compared to those prescribed other anti-seizure medications

Waddy et al, 2019

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Patients with Epilepsy and Coexisting CKD

- Dose reduction may be required when a parent drug or active metabolite is excreted at least 30% unchanged in urine
- Clearance of the drugs by HD may require post-HD dosing because the dialyzability of a drug depends on its protein-binding properties and molecular size
- It is advisable to monitor free serum levels for highly protein-bound drugs such as phenytoin and valproic acid



TABLE 1. Basic pharmacokinetics of AEDs

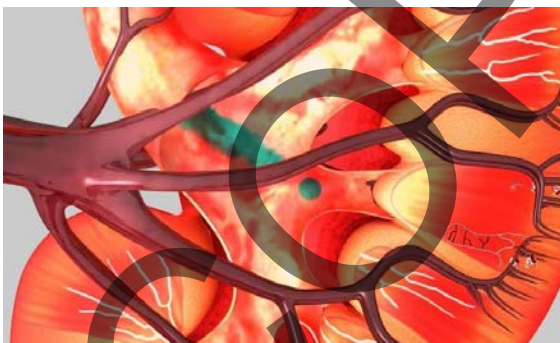
AED	Protein binding	Metabolism	Urinary excretion	Reported renal toxicities
Levetiracetam	<10%	Hydrolysis	66%	Hypokalemia Hypomagnesemia
Valproic acid	90%	Hepatic (CYP450)	1-3%	Tubulointerstitial nephritis Fanconi syndrome Hyponatremia
Lamotrigine	50-55%	Hepatic ^a	10%	AHS with interstitial nephritis
Topiramate	15%	Variable – may depend on coadministration of other AED's	60-70%	Renal tubular (metabolic) acidosis Nephrolithiasis (calcium phosphate)
Zonisamide	40-60%	Hepatic (CYP450)	30-35%	Renal tubular (metabolic) acidosis Nephrolithiasis (calcium phosphate)
Phenytoin	90% Only free fraction is active	Hepatic (CYP450)	<5%	AHS with interstitial nephritis Inhibitor of ADH release
Phenobarbital	50%	Hepatic (CYP450)	25%	AHS with interstitial nephritis Anemia
Carbamazepine	75%	Hepatic (CYP450) Has autoinducer abilities	Negligible	Hypovitaminosis D AHS with interstitial nephritis Hyponatremia
Oxcarbazepine	40%	Hepatic	50%	Hyponatremia
Gabapentin	0%	None	80-95%	Peripheral edema Toxicity may mimic uremic symptoms
Pregabalin	0%	None	> 95%	Peripheral edema Toxicity may mimic uremic symptoms
Lacosamide	<15%	Hepatic (CYP450)	40%	Single reported case of "nephritis"

Seminars in Dialysis—Vol 28, No 4 (July–August) 2015

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AEDs Needing Renal Dosing in CKD

- Eslicarbazepine (600 mg)
- Felbamate (reduce by 50%)
- Gabapentin (100-700 mg)
- Lacosamide (300 mg)
- Levetiracetam (reduce by 50%)
- Oxcarbazepine (reduce by 50%)
- Pregabalin (25-75 mg)
- Primidone (caution)
- Topiramate (reduce by 50%)
- Vigabatrin (reduce by 50-75%)



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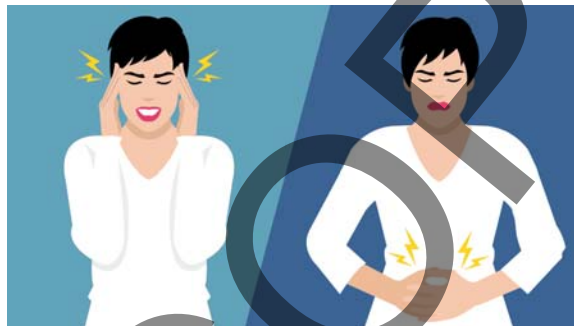
Need for AED Adjustment Post HD

- **No adjustments:**
 - Brivaracetam, Carbamazepine, Clobazam, Perampanel, Valproic acid, phenytoin
- **May need adjustment <30%**
 - Oxcarbazepine, Lamotrigine, Rufinamide, Primidone
- **50% replacement post HD**
 - Levetiracetam, Lacosamide, Phenobarbital, Topiramate, Zonisamide, Vigabatrin, ethosuximide
- **100% replacement post HD**
 - Pregabalin, Gabapentin, eslicarbazepine



AED Effects on Kidney

- ❑ **Nephrolithiasis/ Renal Tubular Acidosis:**
 - Topiramate, Zonisamide and Felbamate
- ❑ **Interstitial Nephritis**
 - Carbamazepine, Lamotrigine, Phenobarbital, Phenytoin, Valproic acid (Fanconi syndrome)
- ❑ **Drug-Induced Lupus Nephritis**
 - Ethosuximide
- ❑ **AHS**
 - Carbamazepine, Lamotrigine, Phenobarbital, Phenytoin
- ❑ **Hyponatremia**
 - Carbamazepine, Eslicarbazepine, Oxcarbazepine, Valproic acid
- ❑ **Hypokalemia and Hypomagnesemia**
 - Levetiracetam
- ❑ **Peripheral Edema (Mimicking Uremic Syndrome)**
 - Pregabalin, Gabapentin



Conclusion

- About 10% of the patients with ESRD may develop seizures
- Keep a low threshold for suspecting seizures in a patient with acute encephalopathy on HD/ Consult Neurology
- Treat the cause of seizure first
- Vigilance is needed with regards to AED management in patients with CKD and Epilepsy



Brain&Kidney
2020

