

Seizures in Children with Cancer

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Overview

- Discuss
 - Epidemiology
 - Pathophysiology
 - Diagnosis
 - Management
 - Prognosis
 - Special situations

Epidemiology

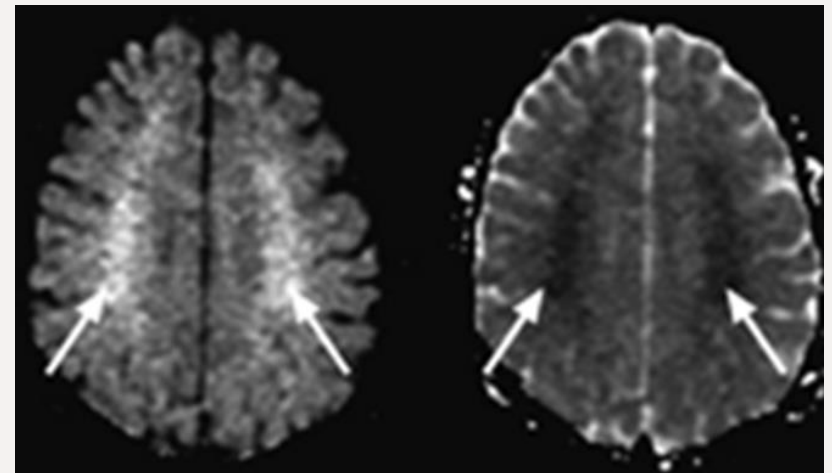
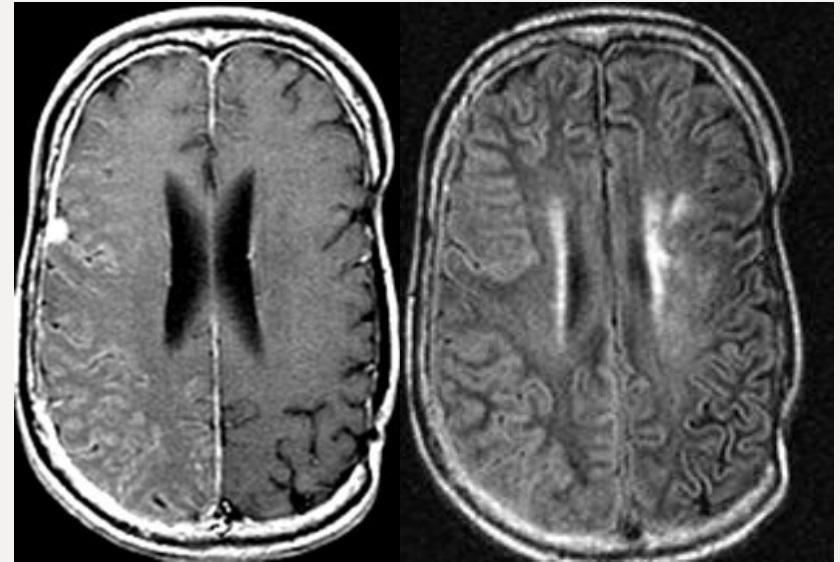
- 9-12% of children with brain tumors
- 12.5% in low grade tumors
- 75-100% in glioneuronal tumors of temporal lobe
- 15-25% prevalence in brain tumors
- 5-20% prevalence during leukemia treatment
- 6% develop late onset epilepsy
 - Ibrahim K, Seizure, 2004
 - Khan RB, Epilepsy Research, 2005
 - Khan RB, J Neurosurg, 2006
 - Packer RJ, J Clin Oncol, 2003

Pathophysiology

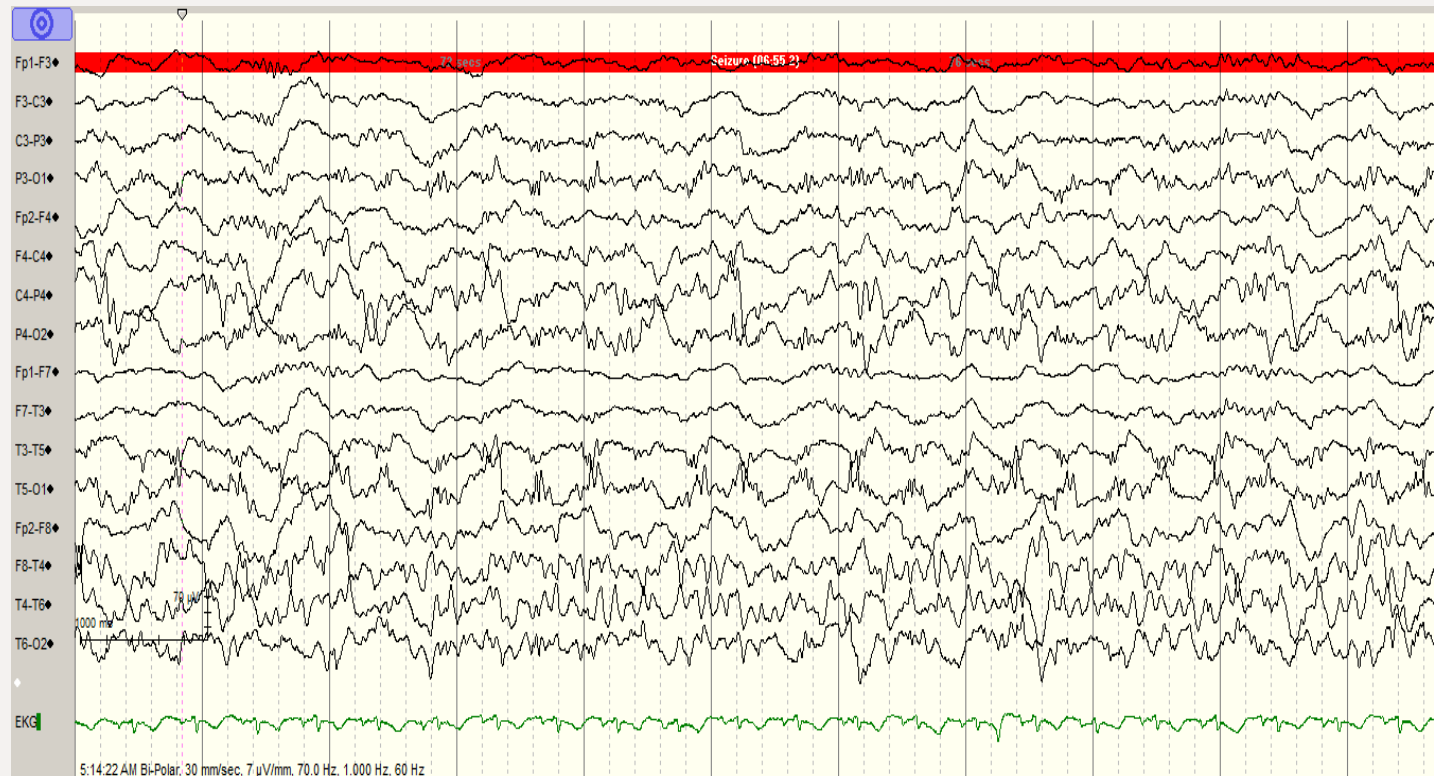
- Abnormal brain structure around tumor
- Cortical dysplasia
- Some molecular alterations, such as BRAF/V600, IDH1/IDH2, mTOR
- Glutamate release and neuronal excitation
- Altered peri-tumor brain networks
- Epileptic neurons within tumor
- Infection or leptomeningeal cancer
- Chemo-toxicity
- Electrolyte dysfunction

Diagnosis

- HISTORY
 - Symptoms
 - Onset
 - Localize
- Imaging
- EEG
 - Routine
 - Extended monitoring



EEG



Finding cures. Saving children.

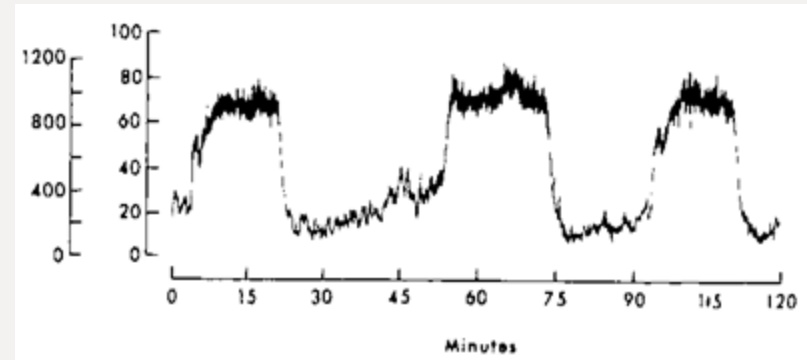
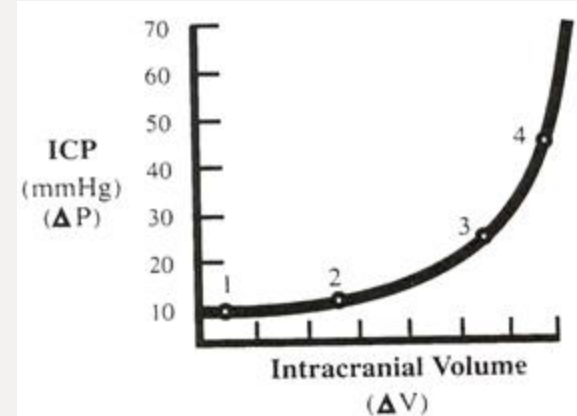
EEG and Chemotherapy

- 39 consecutive ALL patients
- 94 EEGs
- 25 had sharp wave discharges
- 4 had seizures
- All 4 with seizures had abnormal EEG

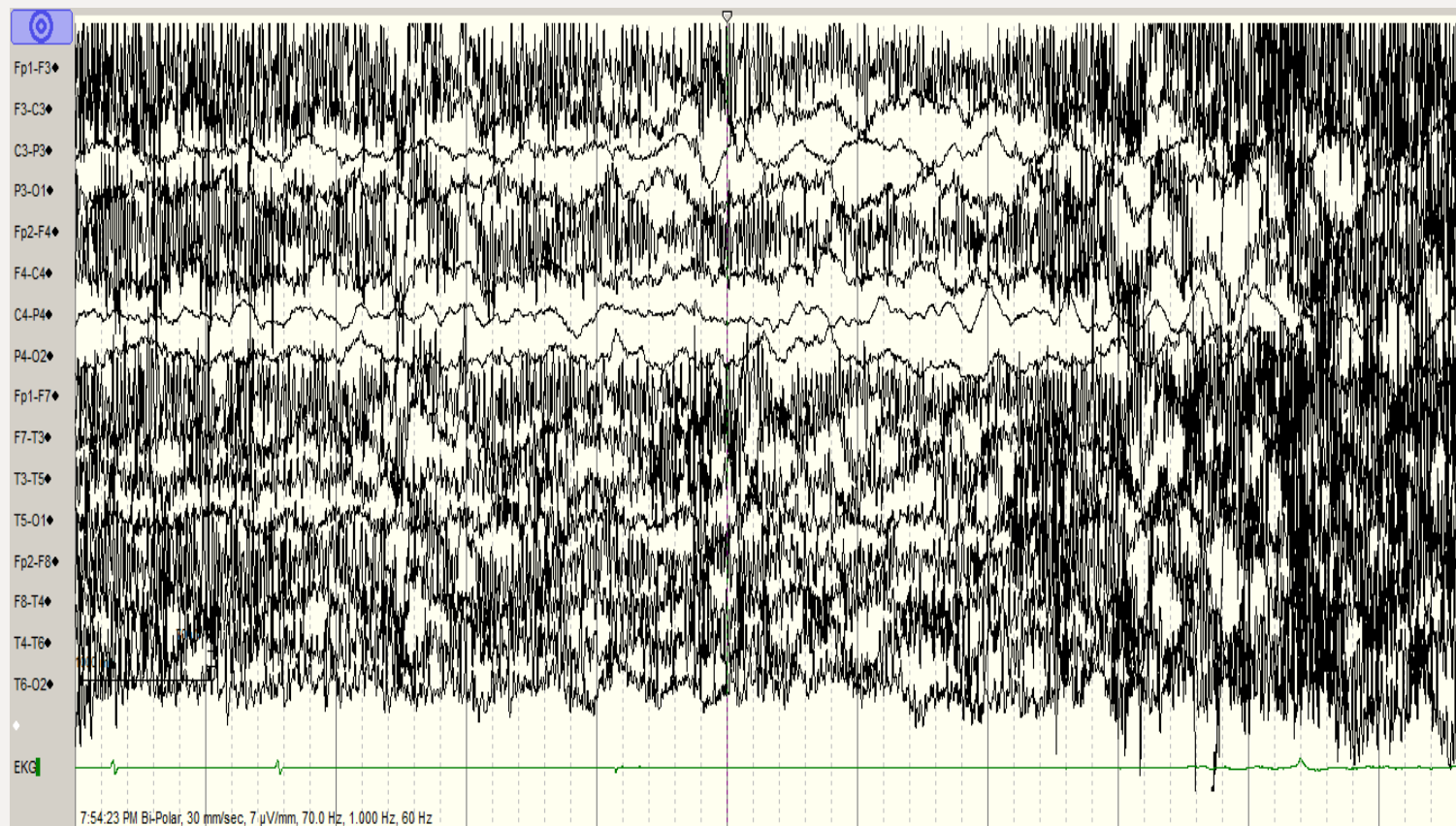
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Seizure mimickers

- TIA
- Migraine Aura
- Methotrexate
Stroke like episodes
- Plateau wave
phenomenon
- Movement disorder
- Syncope



EEG



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First seizure and cancer: treat or not to treat

- 50-80% risk of recurrent seizures with brain tumor
- 55% risk of recurrent tumor during leukemia treatment
- Undetermined recurrence risk in other tumors
 - Khan et al, Epi research, 2005
 - Khan, et al, J Child Neurol, 2014

Special issues concerning anti-convulsant use in cancer patients

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Hepatic enzyme induction

Phenytoin	CYP3A4
Phenobarbital	CYP3A4
Carbamazepine	CYP3A4
Oxcarbazepine	CYP3A4
Primidone	CYP3A4
Lamotrigine	UGT

- Drugs metabolized at CYP3A4
 - Tiagabine
 - Zonisamide
- Inhibition of hepatic enzymes
 - Valproic acid CYP2C19, UGT
 - Topiramate CYP2C19, UGT

- Strong protein binding (>90%)
 - Phenytoin
 - Valproic acid
 - Benzodiazepines
 - Tiagabine
- Moderate protein binding (60-70%)
 - Carbamazepine
 - Phenobarbital
 - Topiramate

- No enzyme induction / protein binding
 - Gabapentin
 - Levetiracetam
 - Lacosamide
- No relevant enzyme induction
 - Lamotrigine
 - Valproic acid
 - Topiramate
 - Zonisamide
- Bone marrow suppression
 - Carbamazepine
 - Valproic acid

Chemo drugs and CYP3A4

- Vinca alkaloids
- Anthracyclines
- Irinotecan
- Taxanes
- VP-16, VM-26
- BCNU
- 9-AC
- Cyclophosphamide / Ifosfamide

Drug interactions

Reduced blood levels or AUC

- | | |
|--------------------|----------------------|
| • Paclitaxel | Fettell et al. 1997 |
| • Cyclophosphamide | William et al, 1999 |
| • Vincristine | Villika et al, 1999 |
| • VP-16 | Rodman et al, 1992 |
| • VM-26 | Balier et al, 1992 |
| • Ifosfamide | Ducharme et al, 1996 |

THE LANCET

Adverse effect of anticonvulsants on efficacy of chemotherapy for acute lymphoblastic leukaemia

Mary V Relling, Ching-Hon Pui, John T Sandlund, Gaston K Rivera, Michael L Hancock,
James M Boyett, Erin G Schuetz, William E Evans

Relling et al

- 716 patients treated over 10 years
- 40 (5.6%) received anticonvulsants for >30 days
- Hazard ratios:

Event free survival	2.67 (1.5, 4.6) p=0.0009
Hematological relapse	3.4 (1.69, 6.88) p=0.0006
CNS relapse	2.90 (1.01, 8.28) p=0.047

Principles of management

- Make a definitive diagnosis
- Goal is complete seizure remission
- Start low dose and build up to desired dose
- Chose non hepatic inducers
- Increment the dose by 20-30% at each breakthrough seizure to tolerance or supratherapeutic level
- Change drug or lower the dose if adverse effects
- Consider adding a second drug if uncontrolled seizures
- Chose a drug which has a different mechanism of action than the first

Principles of management

- Consider referral to an Epilepsy center with expertise for epilepsy brain surgery if therapeutic doses of 2 or 3 drugs fail to control seizures
- If seizure controlled with addition of second drug, then consider weaning first after a reasonable time
- Monitor for adverse effects
- Warn about possibility of depression and suicidal thoughts, driving safety, and teratogenicity
- Monitor levels if concerned about compliance or dose adjustments
- Okay to have supratherapeutic levels if no clinical toxicity, or sub-therapeutic levels if controlled

Drugs of choice

- Levetiracetam
- Lacosamide
- Gabapentin
- Pregabalin
- Lamotrigine
- Zonisamide
- Topiramate*
- Oxcarbazepine*

Drugs to be avoided

- Phenytoin
- Phenobarbital
- Carbamazepine
- Prempanel
- Valproic acid*
- Oxcarbazepine*

Seizure outcome brain tumors

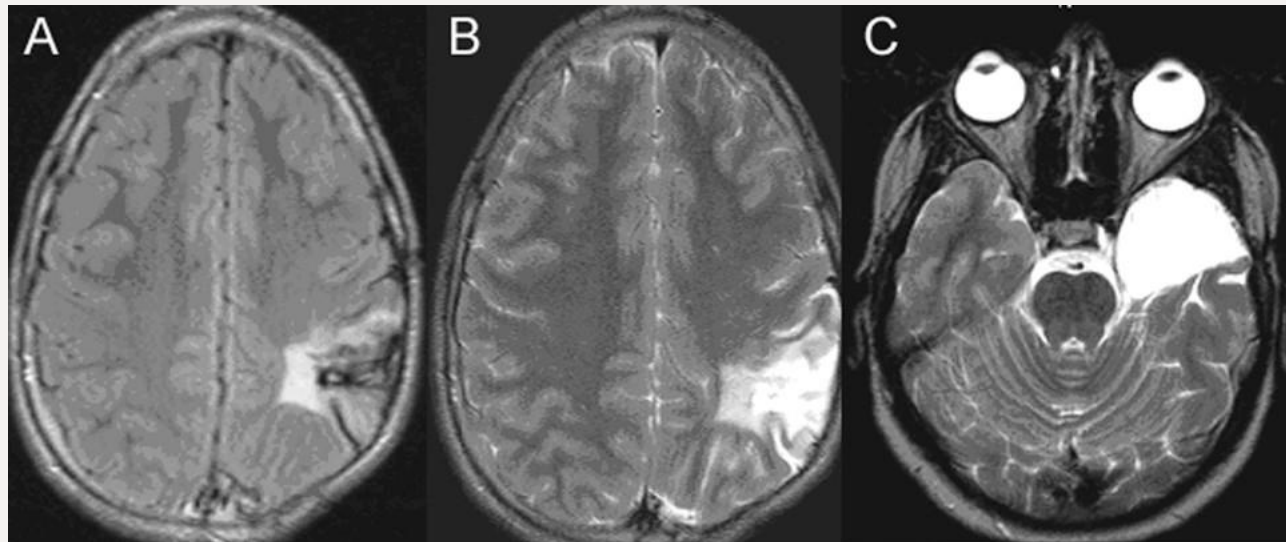
Khan et al, Epi Research, 2005

- Total 157
- Median follow-up 3.3 years
- Controlled 65%
 - Mono/No therapy 93%
 - 2 AEDs 7%
- Partially controlled 18%
 - Mono/No therapy 54%
 - 2 AEDs 39%
 - ≥ 3 AEDs 7%
- Intractable 17%
 - Monotherapy 46%
 - 2 AEDs 38%
 - ≥ 3 AEDs 16%

Risk factors for poor seizure outcome

Variable	Uncontrolled	Intractable
< 3-years	>0.05	>0.05
No. of seizures	>0.05	>0.05
No. BTS	>0.05	>0.05
Focal deficits	0.03	>0.05
Chemo	>0.05	>0.05
RT	>0.05	>0.05
VPS	>0.05	>0.05
Residual tumor	>0.05	>0.05
High grade	0.09	>0.05
T-2 hyperintens	0.0001	0.008
Leucoenceph	>0.05	>0.05
Sharp & Spikes	>0.05	>0.05
Slow waves	0.04	>0.05
Location	>0.05	>0.05

Peri-cavity T2-hyperintensity



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Seizure outcome in children with acute leukemia

Khan et al, J Child Neurol, 2014

- Total 62
- Median follow-up 6.5 years
- Controlled seizures 44 (71%)
- Intractable 10 (16%)
(Secondary Lennox Gastaut, Khan, JCN, 2002)
- Partially controlled 8 (13%)
- Off AED 32 (52%)
- Seizure recurrence 8 (25%)

Risk factors for poor seizure control in ALL patients

- Uncontrolled seizures
 - Age <3-years at Dx 0.004
 - Focal neurologic deficits 0.04
 - H/O relapse 0.03
- Intractable seizures
 - Age <3yrs at Dx 0.004
 - EEG slow waves 0.007

Khan et al,, J Child Neurol 2014

When to withdraw seizure medications

- Consider wean if no seizure for six months after complete tumor resection
- Consider wean at conclusion of toxic chemotherapy and seizure free status >6-months.
- Consider wean earlier if only few seizure with PRES
- Like to have 12-24 months of seizure free status before considering withdrawal in brain tumor patients

Risk factors for seizure recurrence after AED withdrawal

- Brain tumor
 - >1 tumor resection $p=0.0007$
 - Younger age at tumor dx $p=0.05$
 - Whole brain RT $p=0.007$
 - >1 AED $p=0.07$
 - EEG $p=>0.1$
 - Posterior fossa tumor $p=0.001$
 - Low grade histology $p=0.07$
- ALL
 - Poor response to first AED $p=0.04$

Khan et al, J Child Neurol, 2014

Khan et al, Epilepsia, 2006

Special situations

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Status Epilepticus

- Definition

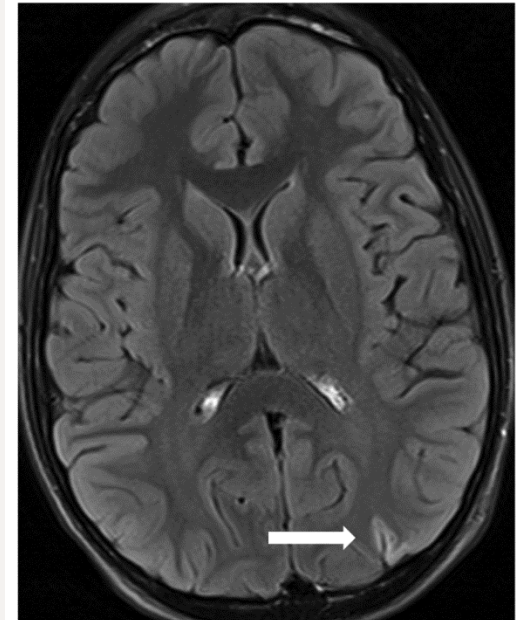
Continuing seizure for 3-5 minutes, or back to back seizures without return of consciousness between them, or continuing electrographic seizure

- Convulsive

- Focal
- Generalized tonic, clonic, or tonic-clonic
- High risk for respiratory compromise
- Risk of muscle break down and renal failure

Status epilepticus

- Non convulsive
 - Full recovery possible even after days of continuing seizure activity
 - Laminar necrosis may develop
 - Management is more controversial
 - Primary
 - Sudden mental status change w/wo minor motor twitching
 - Following convulsive seizure
 - Failure to recover consciousness as expected



Principals of management

- Establish IV access
- Protect airway
- Benzodiazepine use
- Transfer to ICU
- Check and monitor electrolytes, including CPK and glucose
- Follow treatment protocol
- Establish and treat cause
- Monitor heart rate and BP

St. Jude drug protocol

Stage	Drug	Dose
First May be repeated 2-3 times	Lorazepam Midazolam Diazepam	0.05-0.1 mg/kg IV 0.2 mg/kg IV/IM 0.3 mg/kg IV
Second	Levetiracetam	30 mg/kg IV over 30-60 minutes May repeat 10/mg/kg
Third	Fosphenytoin	20 mg/kg over 15-30 min May repeat 10 mg/kg
Fourth	General anesthesia to burst suppression on EEG* Ionotrope support	Midazolam Pentobarbital Thiopental Propofol

Burst suppression



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Additional workup

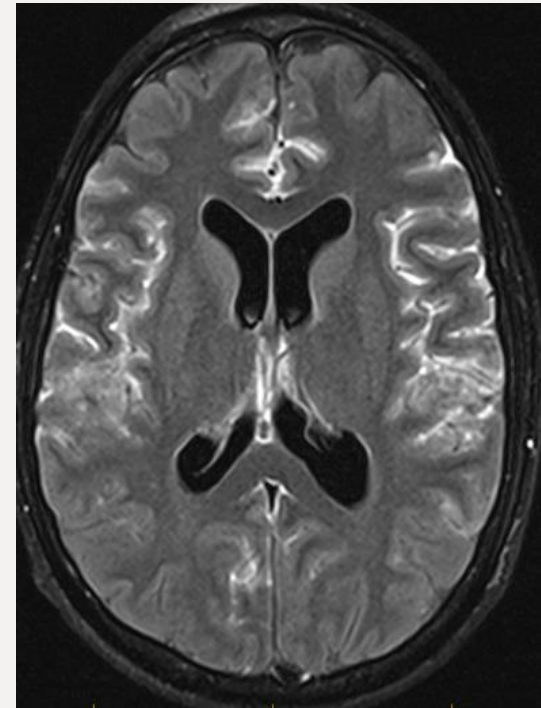
- Calcium, magnesium, CPK, cultures, viral studies
- Imaging – CT/MRI
- CSF
 - Protein, glucose, cell count
 - Bacterial and fungal staining
 - Bacterial / viral serology (PCR)
 - TB, Toxo, others

Supportive care

- Respiratory management
- Antibiotics and anti virals
- Fluids
- Ionotropes
- Electrolytes
- Watch for rhabdomyolysis

Refractory status epilepticus

- 20-25% of all status epilepticus
- Increased morbidity and mortality
- Commonly associated with an underlying cause
 - Encephalitis (Infection or immune mediated)
 - Leptomeningeal cancer
 - Electrolyte dysfunction



Management of refractory status epilepticus

- Add additional drugs and take them to supra therapeutic levels
- Combine drugs with different mechanisms of action
- Drugs to consider
 - Lacosamide
 - Topiramate
 - Valproic acid
 - Clobazam

