The Annual General Pediatric Review & Self-Assessment

Nicklaus Children's Hospital

Neurology

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Disclosure of Relevant Relationship

Dr. Jayakar has not had (in the past 24 months) any relevant conflicts of interest or relevant financial relationship with the manufacturers of products or services that will be discussed in this CME activity or in his presentation.

Dr. Jayakar will support this presentation and clinical recommendations with the “best available evidence” from medical literature.

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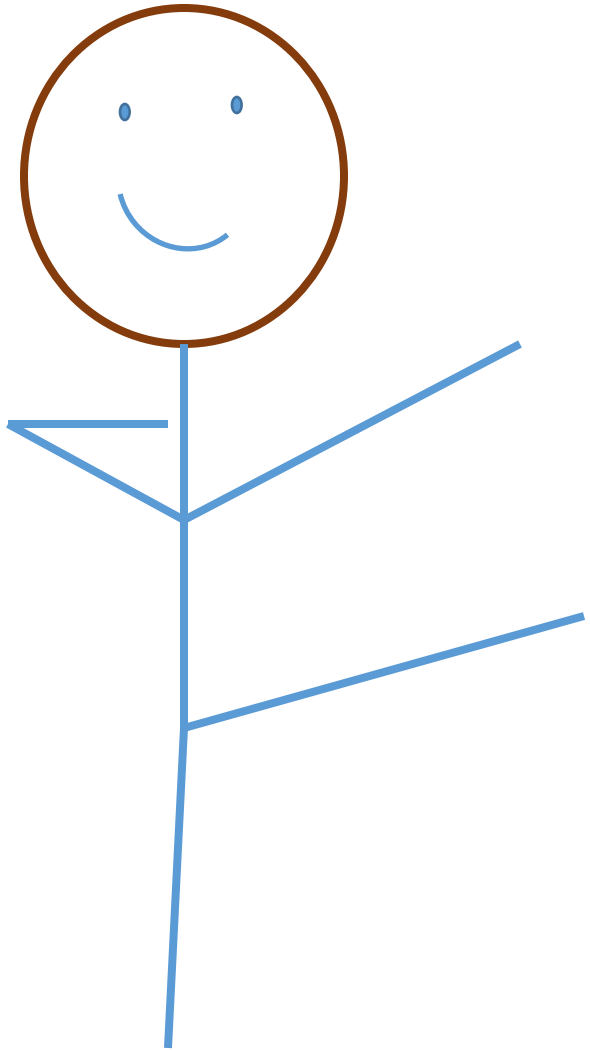
Neurology Summary

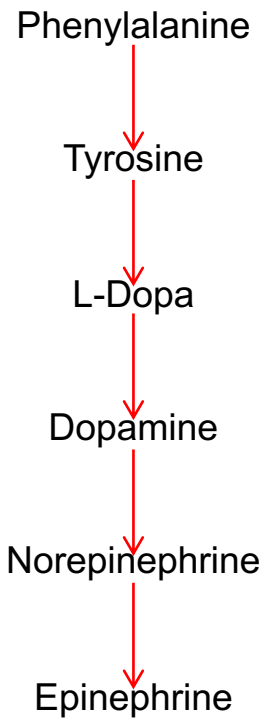


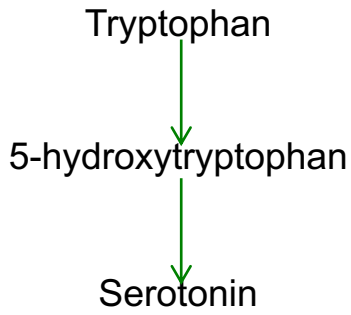
- Basic Neuroanatomy
- Seizures
- Meningitis and Encephalitis
- Hypotonia/Neuromuscular Disorders
- Inflammatory Neuropathies
- Cerebrovascular accident
- Headaches
- Psychiatry
  - Mood Disorders
  - Delirium
  - Psychosomatic disorders
  - Behavioral and developmental disorders

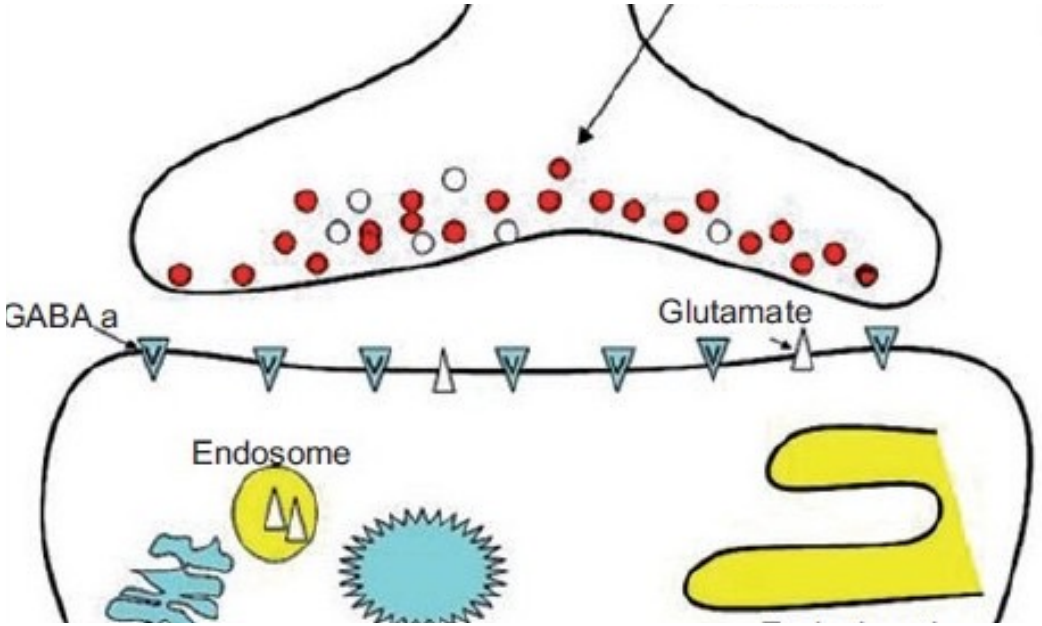
Basic Neuroanatomy

Anatomical Structure	Neurologic Conditions Associated	Symptoms and Deficits
Temporal lobes	HSV infection, limbic encephalitis	Seizures, altered mental status, memory dysfunction
Frontal and Parietal lobes	Infectious encephalitis, ADEM, MCA stroke	Seizures, altered mental status, focal motor/sensory deficits
Occipital lobes	PRES, PCA stroke	Visual field loss, Altered mental status, seizures
Basal ganglia/thalamus	Hypoxic ischemic injury	Coma, spasticity, tone abnormalities, movement disorders
Cerebellum	Posterior fossa tumors, Cerebellitis, post infectious cerebellar ataxia	Dysmetria, nystagmus, gait instability, loss of tone
Brain stem	Posterior fossa tumor, demyelinating disease (NMO)	Ophthalmoplegia, bulbar paralysis, respiratory difficulty, coma

Neurotransmitters & Neurotransmission

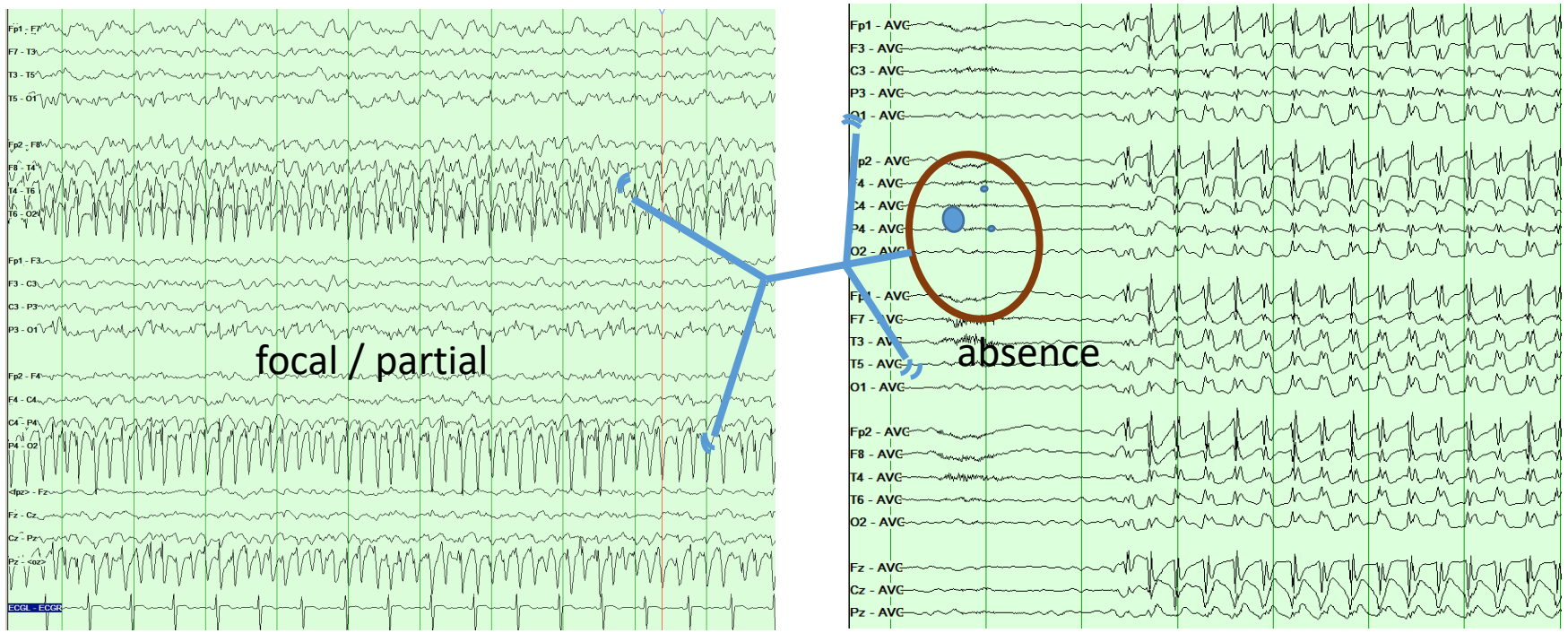






Glutamate - major EXCITATORY
GABA - major INHIBITORY

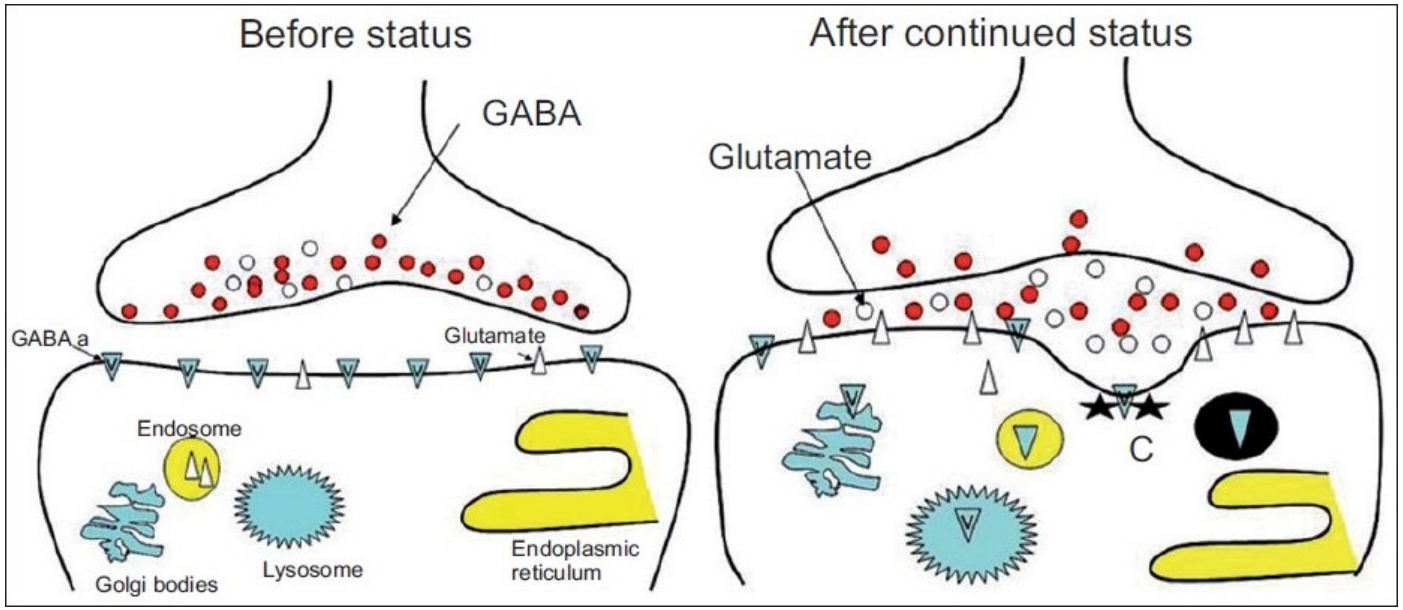
Seizures

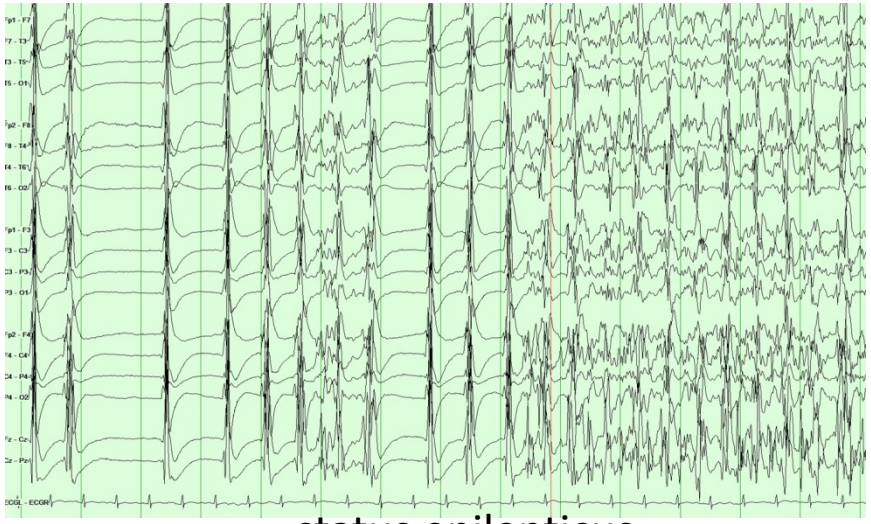


Common reasons in children:

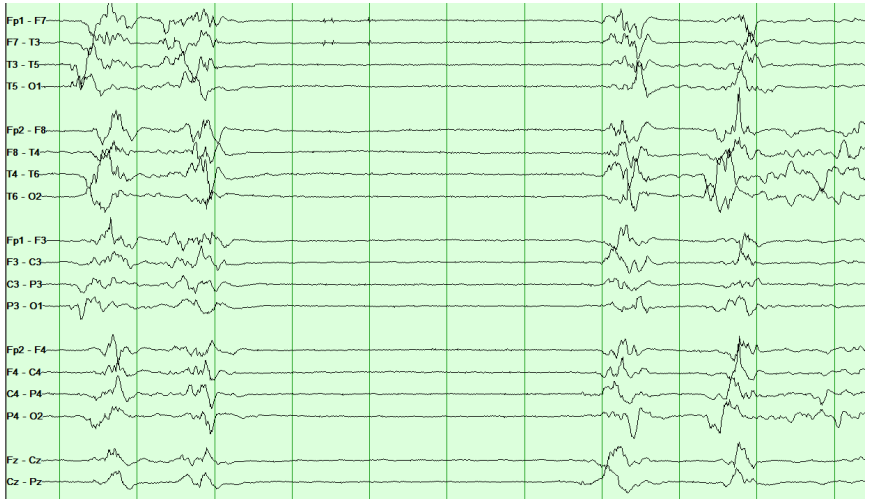
- Febrile seizures
- Non-adherence to medication in an epilepsy patient
- Infections
- Symptomatic causes (genetic defects, remote HIE)

Seizures: Status Epilepticus





status epilepticus



burst suppression

Rationale for treatment

- >30 minute may lead to permanent neuronal injury
- If not treated by 5 minutes, more difficult to stop
- Don’t want to over treat brief self resolving seizures
- Status treatment protocols use a 5 minute definition

Time Line

Interventions for emergency department, in-patient setting, or prehospital setting with trained paramedics

0-5 min Stabilization phase

1. Stabilize patient (airway, breathing, circulation, disability - neurologic exam)
2. Time seizure from its onset, monitor vital signs
3. Assess oxygenation, give oxygen via nasal cannula/mask, consider intubation if respiratory assistance needed
4. Initiate ECG monitoring
5. Collect finger stick blood glucose. If glucose < 60 mg/dl then
   Adults: 100 mg thiamine IV then 50 ml D50W IV
   Children ≥ 2 years: 2 ml/kg D25W IV Children < 2 years: 4 ml/kg D12.5W
6. Attempt IV access and collect electrolytes, hematology, toxicology screen, (if appropriate) anticonvulsant drug levels

5-20 min Initial therapy phase

<u>A benzodiazepine is the initial therapy of choice (Level A)</u>:

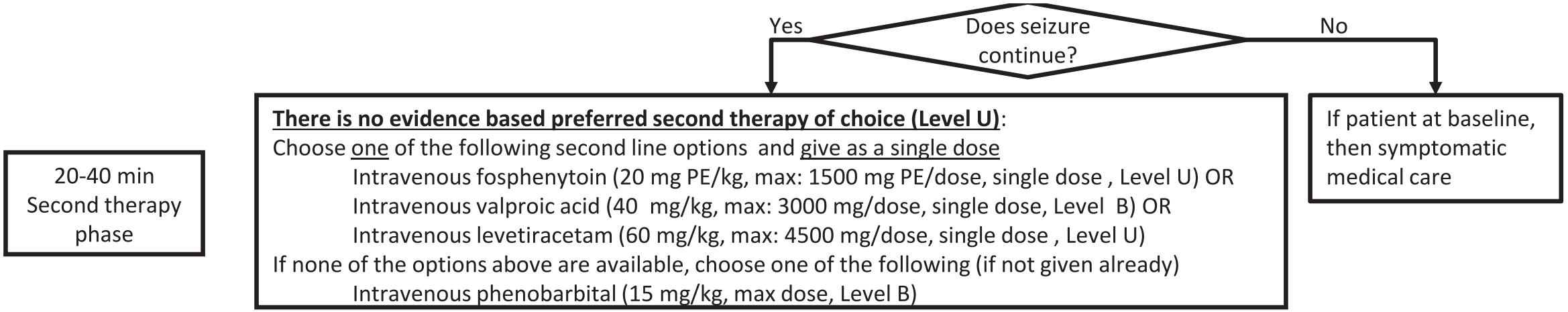
Choose <u>one</u> of the following 3 equivalent first line options with dosing and frequency:

- Intramuscular midazolam (10 mg for > 40 kg, 5 mg for 13-40 kg, single dose, Level A) OR
- Intravenous lorazepam (0.1 mg/kg/dose, max: 4 mg/dose, may repeat dose once, Level A) OR
- Intravenous diazepam (0.15-0.2 mg/kg/dose, max: 10 mg/dose, may repeat dose once, Level A)

If none of the 3 options above are available, choose one of the following:

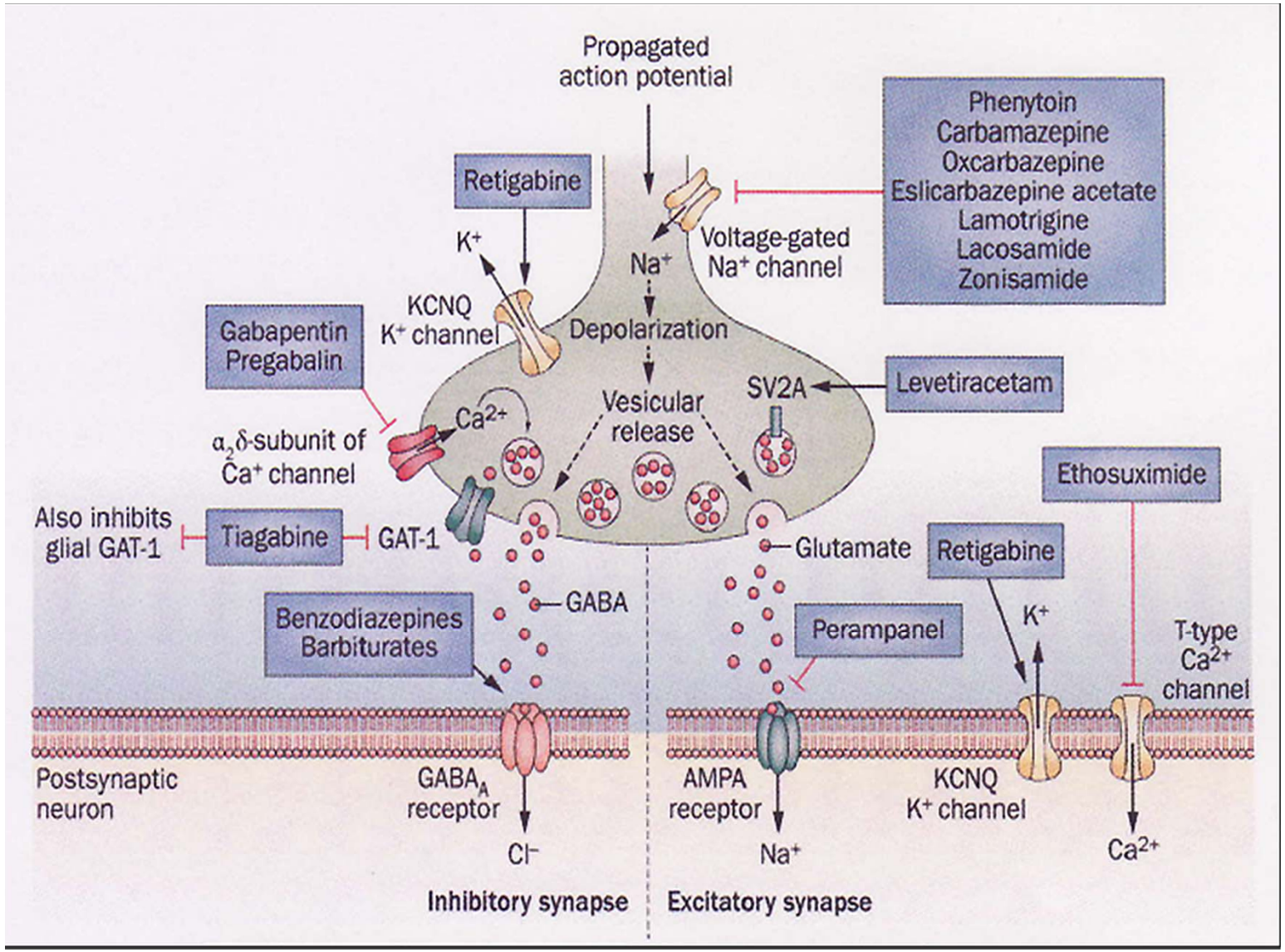
- Intravenous phenobarbital (15 mg/kg/dose, single dose, Level A) OR
- Rectal diazepam (0.2-0.5 mg/kg, max: 20 mg/dose, single dose, Level B) OR
- Intranasal midazolam (Level B), buccal midazolam (Level B)

If patient at baseline, then symptomatic medical care

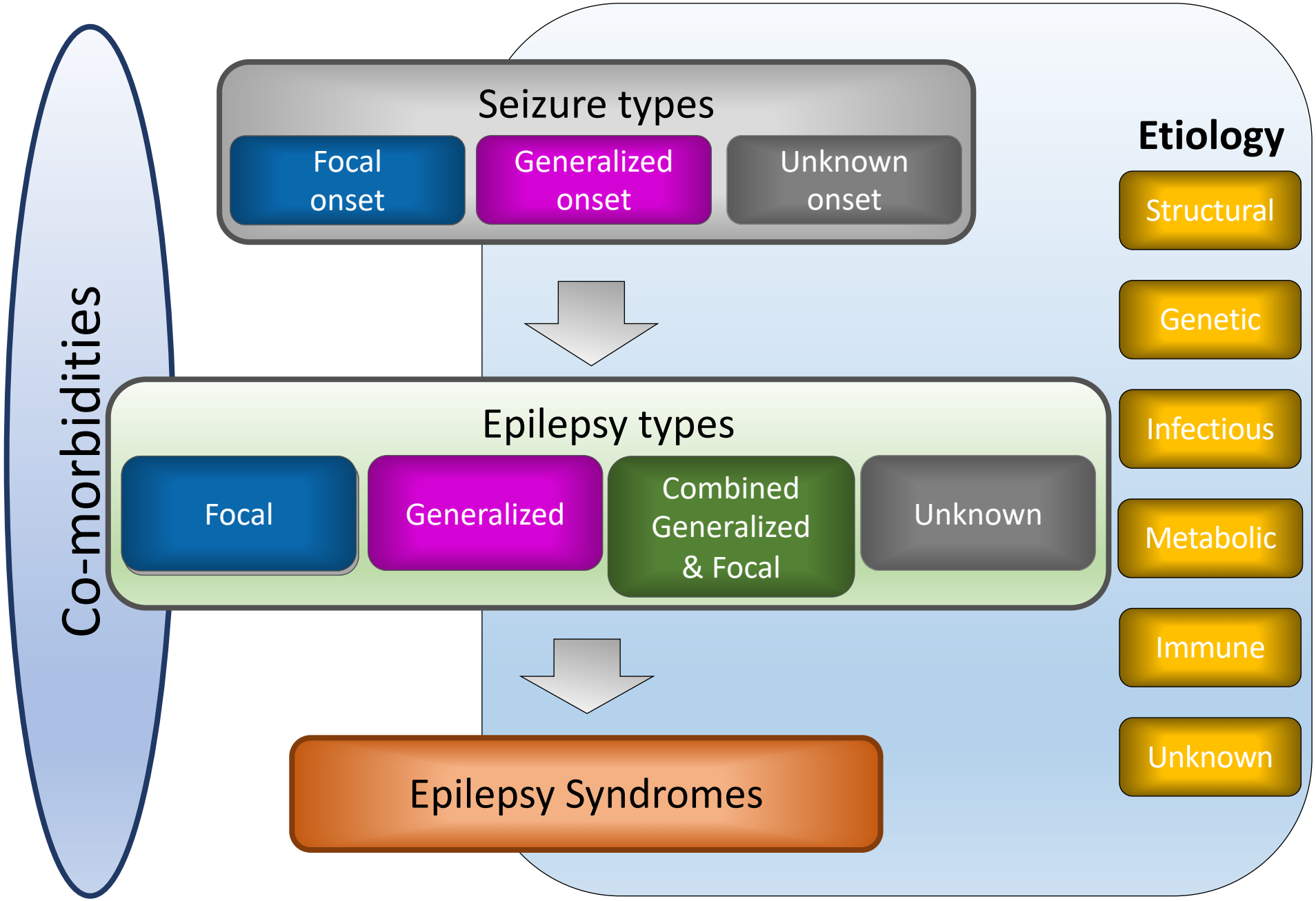

Yes
Does seizure continue?
No
20-40 min
Second therapy phase
There is no evidence based preferred second therapy of choice (Level U):
Choose one of the following second line options and give as a single dose
Intravenous fosphenytoin (20 mg PE/kg, max: 1500 mg PE/dose, single dose , Level U) OR
Intravenous valproic acid (40 mg/kg, max: 3000 mg/dose, single dose, Level B) OR
Intravenous levetiracetam (60 mg/kg, max: 4500 mg/dose, single dose , Level U)
If none of the options above are available, choose one of the following (if not given already)
Intravenous phenobarbital (15 mg/kg, max dose, Level B)
If patient at baseline, then symptomatic medical care

Recommendations- Third Phase Therapy

- No clear evidence to guide therapy
- Efficacy drops following each stage of therapy
- Can consider repeat AED or usage of anesthetic



Loscher and Schmidt, Nature Reviews Neurology 2012


Co-morbidities
Seizure types
Focal onset
Generalized onset
Unknown onset
Epilepsy types
Focal
Generalized
Combined Generalized & Focal
Unknown
Epilepsy Syndromes
Etiology
Structural
Genetic
Infectious
Metabolic
Immune
Unknown

Infantile spasms vs West Syndrome

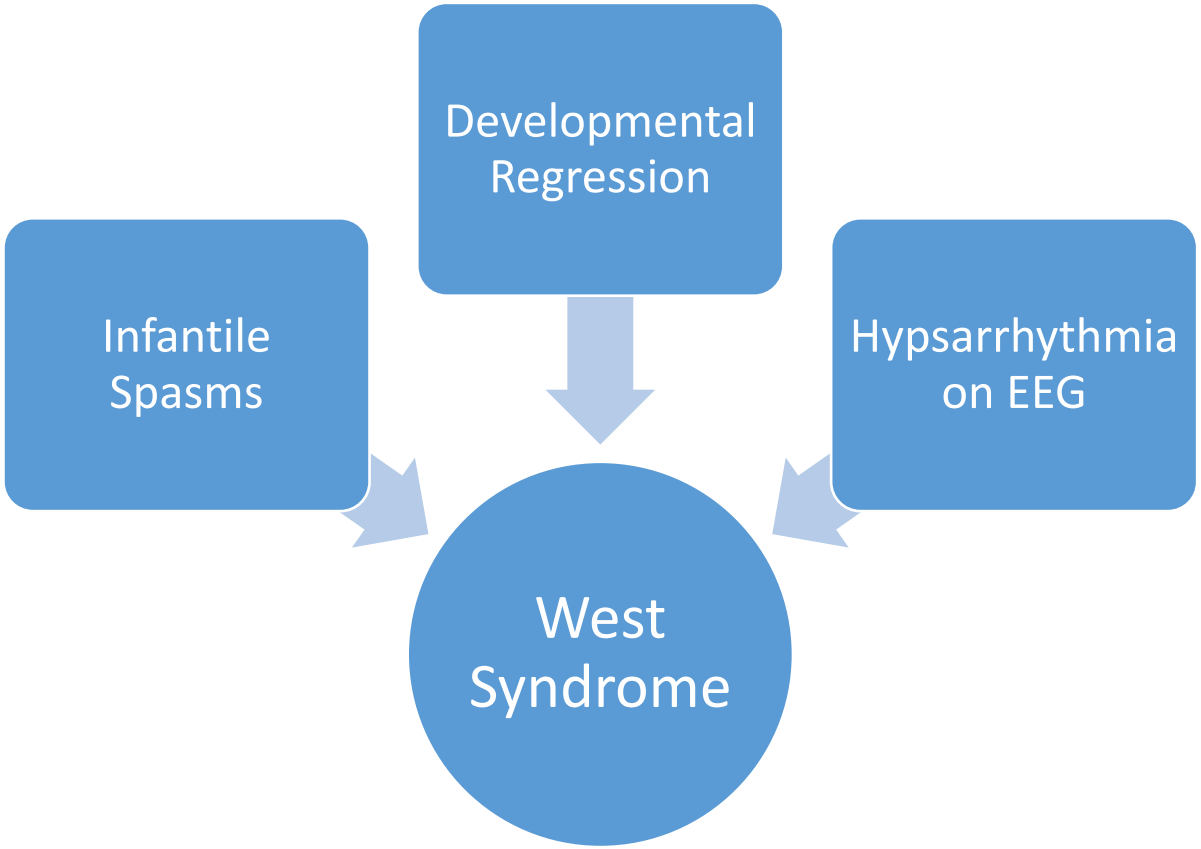


TABLE 20.1

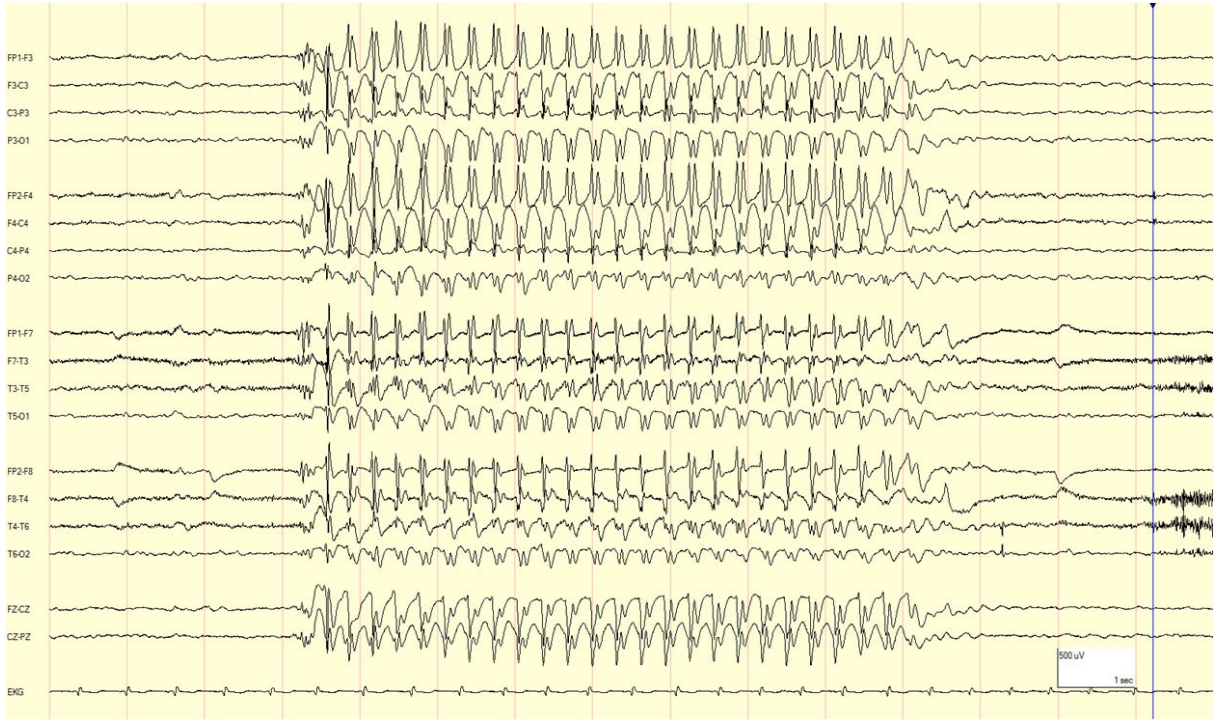
SUMMARY OF THE ENCEPHALOPATHIC GENERALIZED EPILEPSY SYNDROMES

Syndrome vs. clinical features	Lennox–Gastaut syndrome (4,10,14)	Myoclonic-astatic epilepsy (2,14,19)	Severe myoclonic epilepsy of infancy (10,18,20)
Clinical seizure types	Atypical absence (75%), tonic–atonic seizures (75%), myoclonic (30%), partial (15%), and GTC (7%) seizures	Myoclonic, myoclonic-astatic seizures, partial seizures rare	Febrile seizures followed by afebrile U/L clonic and GTC seizures. Later myoclonic, atypical absence, and complex partial.
MRI	Normal or nonspecific abnormal	Normal	Normal
Interictal EEG pattern	Awake = SSW Asleep = GPFA Background with diffuse slowing often multifocal spikes	GSW, often mixture of SSW and fast (>3 Hz) GSW	Multifocal and generalized spikes; PPR in 40%
Course	Often severe mental retardation	50% with resolution of seizures in 3 y and 50% with normal IQ	Mental retardation, persistent seizures
Prognosis	Progressive deterioration despite broad spectrum AEDs	Often stabilizes with AEDs after the first 3 y, often dramatic response to ketogenic diet	Progressive deterioration initially followed by a static phase

GTC, generalized tonic–clonic; U/L, unilateral; PPR, photoparoxysmal response; GPFA, generalized paroxys
AED, antiepileptic drugs; CSWS, continous spike and wave during slow wave sleep; LKS, Landau Kleffner S

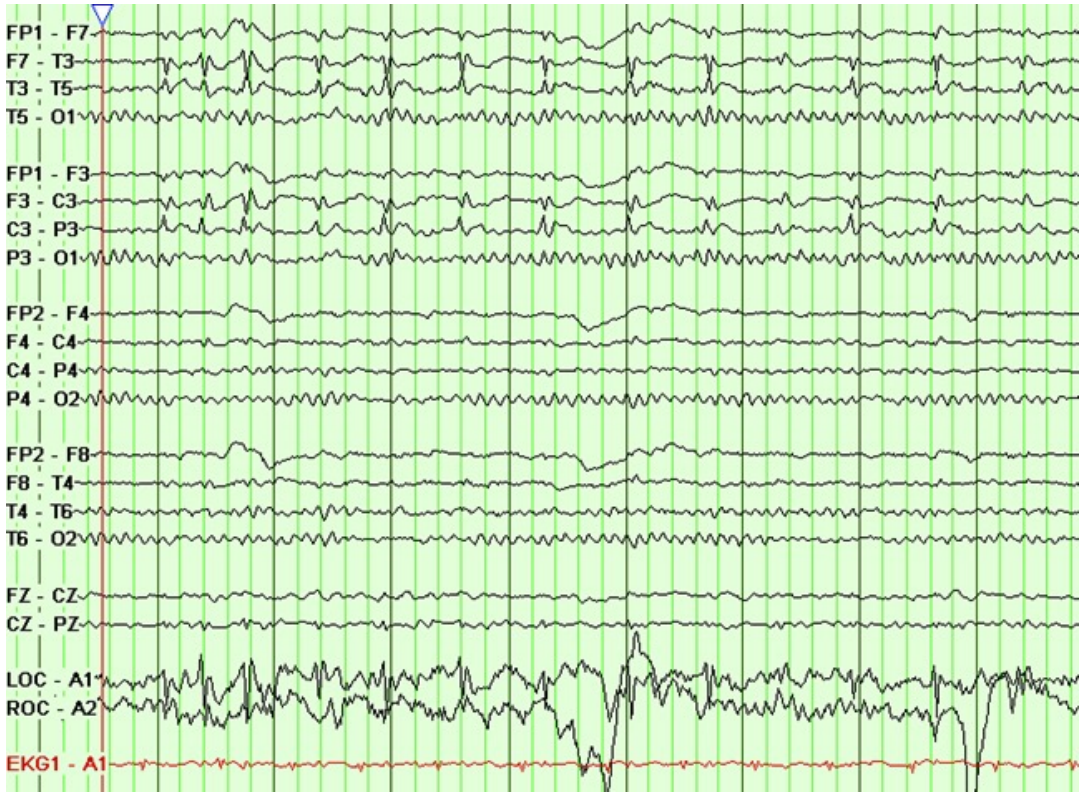
Idiopathic Generalized Epilepsy

- 3 primary seizures types
  - Absence seizures
    - unresponsiveness of short duration with potential eye fluttering or automatisms
    - No postictal phase, although patients cannot remember event
    - 3hz spike and wave on EEG
  - Myoclonic seizures
    - Brief jerks of the extremities or trunk
    - No alteration of consciousness
  - Generalized tonic clonic seizures



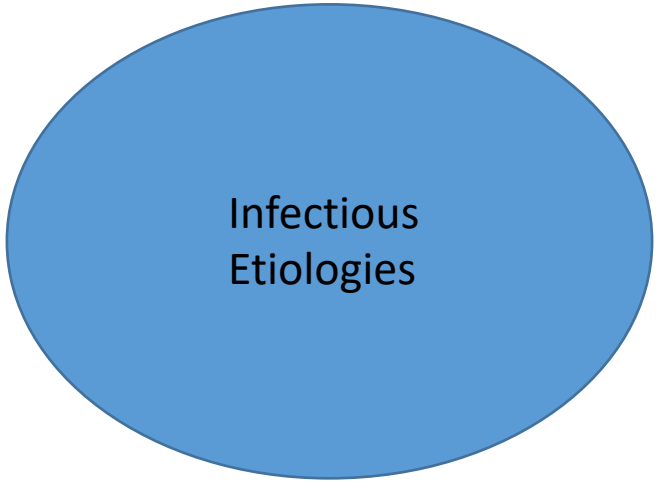
Benign Epilepsy with Centrotemporal Spikes (BECTS)

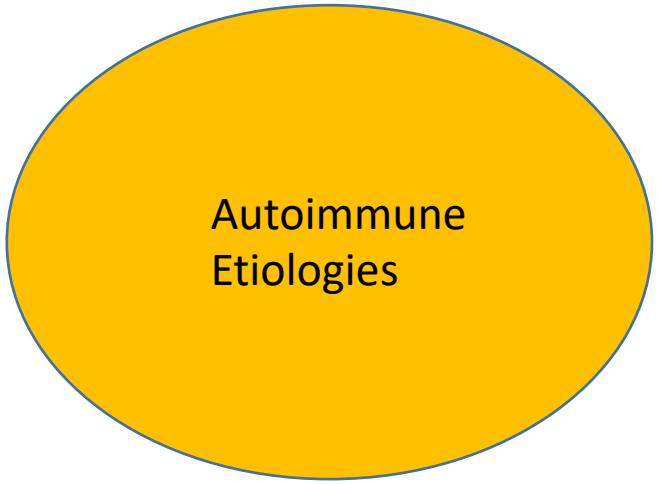
- 3-13yo, more common in males
- Seizures typically shortly after falling asleep or awakening
  - Lower face movements or sensory changes
  - Hemibody convulsions
  - Can evolve into GTCs
- EEG shows sleep potentiated centrotemporal spikes



Encephalitis

- Debilitating neurological disorder
- “Encepha” – brain, “Itis”- inflammation → Rapidly progressive encephalopathy
- 5-10 per 100,000 inhabitants





Core Symptoms

- Changes in level of consciousness or behavior
- Fever
- New focal CNS findings
- CSF pleocytosis
- Seizures or EEG alterations
- MRI changes

Table 1 Diagnostic criteria for encephalitis[a]

Major criterion (required)
Patients presenting to medical attention with altered mental status (defined as decreased or altered level of consciousness, lethargy, or personality change) lasting ≥24 hours with no alternative cause identified
Minor criteria (2 required for possible encephalitis; ≥3 required for probable or confirmed encephalitis)
Documented fever ≥38°C (100.4°F) within the 72 hours before or after presentation
Generalized or partial seizures not fully attributable to a preexisting seizure disorder
New onset of focal neurologic findings
CSF leukocyte count ≥5/mm^3
Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset
Abnormality on EEG that is consistent with encephalitis and not attributable to another cause.

[a] Adapted from reference 7 (Venkatesan et al. *Clinical Infectious Diseases* 2013;57:1114-1128) by permission of Oxford University Press on behalf of the Infectious Diseases Society of America.

Routine studies
CSF (unless contraindicated[b])
Opening pressure, leukocyte count with differential, erythrocyte count, protein, glucose
Gram stain and bacterial culture
HSV-1/2 PCR (if test available, consider HSV CSF IgG and IgM in addition)
VZV PCR (sensitivity may be low; if test available, consider VZV CSF IgG and IgM in addition)
Enterovirus PCR
Cryptococcal antigen or India ink staining
Oligoclonal bands and IgG index
Venereal Disease Research Laboratory
Serum
Routine blood cultures
HIV serology (consider RNA)
Treponemal testing (rapid plasma reagin, specific treponemal test)
Imaging
Neuroimaging (MRI preferred to CT, if available)
Chest imaging (chest x-ray or CT)
Neurophysiology
EEG
Other tissues/fluids
When clinical features of extra-CNS involvement are present, we recommend additional testing (e.g., biopsy of skin lesions; bronchoalveolar lavage or endobronchial biopsy in those with pneumonia/pulmonary lesions; throat swab PCR/culture in those with upper respiratory illness; stool culture in those with diarrhea); also see below

Bacterial vs Viral Encephalitis

		Bacterial	Viral
Symptoms		Stiff neck (77%), vomiting (82%), and fever (94%) key symptoms	Headache, fever, vomiting, seizures, altered mental status
LP	WBC	↑↑	↑ lymphocytic predominance
	Protein	↑↑	↑ or normal
	Glucose	↓↓	↓ or normal
EEG		Seizures w/ cerebritis/encephalitis	Focal spikes or slowing
MRI		meningeal or cortical enhancement, brain abscess	T2 cortical hyperintensities, cerebral edema - HSV- temporal lobes - Basal ganglia- EBV or Japanese encephalitis - Substantia nigra, brainstem, spinal cord- WNV
Treatment		Broad spectrum abx with CSF penetration	Acyclovir

Autoimmune Encephalitis

- Associated with antibodies against neuronal cell surface or synaptic proteins
- Can resemble infectious encephalitis
- Neurological and psychiatric manifestations w/o fever and CSF pleocytosis
- Can occur as result of oncologic process → paraneoplastic syndrome

Panel 1: Diagnostic criteria for possible autoimmune encephalitis

Diagnosis can be made when all three of the following criteria have been met:

1 Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status*, or psychiatric symptoms

2 At least one of the following:
- New focal CNS findings
- Seizures not explained by a previously known seizure disorder
- CSF pleocytosis (white blood cell count of more than five cells per mm^3)
- MRI features suggestive of encephalitis†

3 Reasonable exclusion of alternative causes (appendix)

*Altered mental status defined as decreased or altered level of consciousness, lethargy, or personality change. †Brain MRI hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter, or both compatible with demyelination or inflammation.

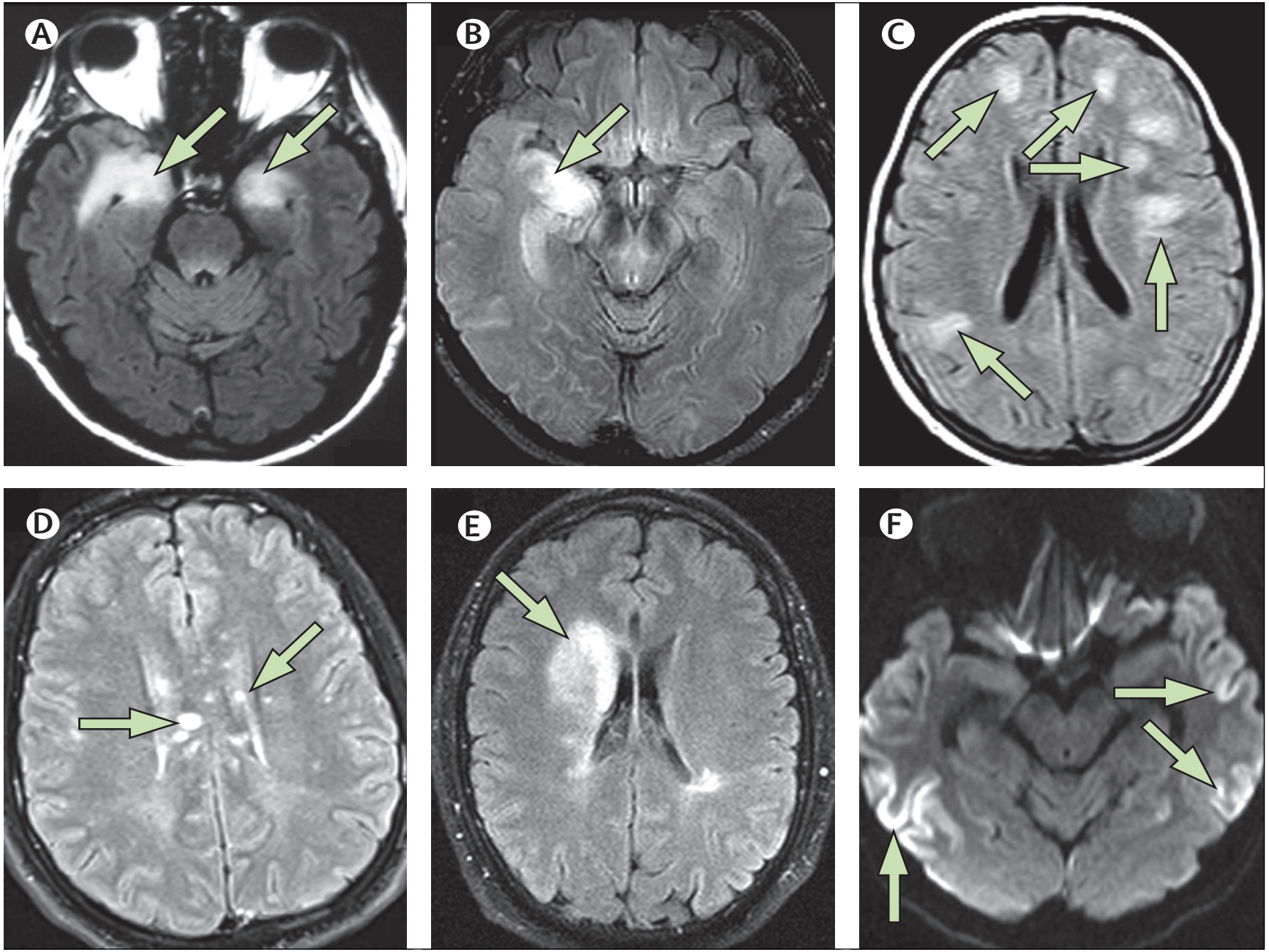
Acute Disseminated Encephalomyelitis (ADEM)

- Monophasic inflammatory disease
- Can be preceded by infection or vaccination
- Encephalopathy plus other CNS symptoms
  - CN palsies
  - ON
  - Ataxia
  - Hemiparesis
- CSF pleocytosis (WBC <50), but w/o OCB
- MRI- multiple large (>2cm) abnormalities on T2/FLAIR

Panel 3: Diagnostic criteria for definite acute disseminated encephalomyelitis[32]

Diagnosis can be made when all five of the following criteria have been met:

1. A first multifocal, clinical CNS event of presumed inflammatory demyelinating cause
2. Encephalopathy that cannot be explained by fever
3. Abnormal brain MRI:
   - Diffuse, poorly demarcated, large (>1–2 cm) lesions predominantly involving the cerebral white matter
   - T1-hypointense lesions in the white matter in rare cases
   - Deep grey matter abnormalities (eg, thalamus or basal ganglia) can be present
4. No new clinical or MRI findings after 3 months of symptom onset
5. Reasonable exclusion of alternative causes


A
B
C
D
E
F

NMDA Encephalitis

- Antibodies against Anti-GluN1 subunit of NMDA receptor
- 1/3 < 18yo, F:M is 4:1
- Associated with tumors although less frequent in children (5% vs 60% in adults)
- Present with abnormal behavior, irritability, insomnia, followed by dyskinesia, speech dysfunction, autonomic instability, altered consciousness, and seizures
- Seizures more common in young children
- Can present after HSV infection

Panel 4: **Diagnostic criteria for anti-NMDA receptor encephalitis**

Probable anti-NMDA receptor encephalitis*

Diagnosis can be made when all three of the following criteria have been met:

1 Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms:
   - Abnormal (psychiatric) behaviour or cognitive dysfunction
   - Speech dysfunction (pressured speech, verbal reduction, mutism)
   - Seizures
   - Movement disorder, dyskinesias, or rigidity/abnormal postures
   - Decreased level of consciousness
   - Autonomic dysfunction or central hypoventilation

2 At least one of the following laboratory study results:
   - Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)
   - CSF with pleocytosis or oligoclonal bands

3 Reasonable exclusion of other disorders (appendix)

Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma

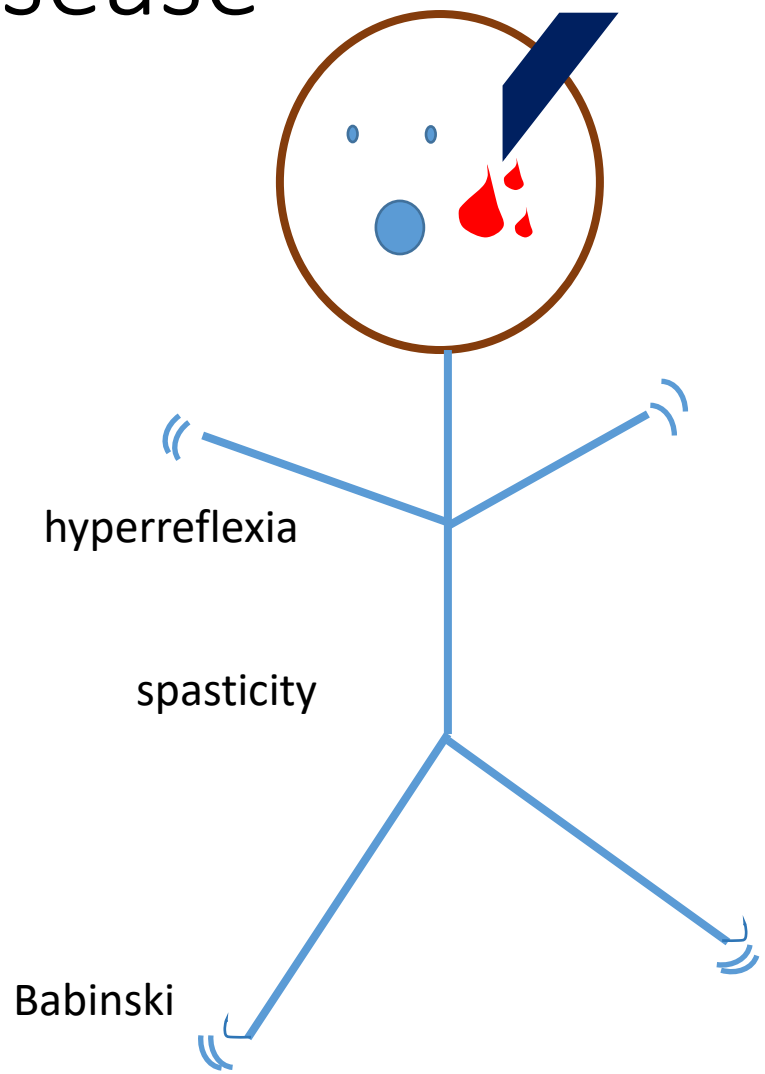
Definite anti-NMDA receptor encephalitis*

Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies,† after reasonable exclusion of other disorders (appendix)

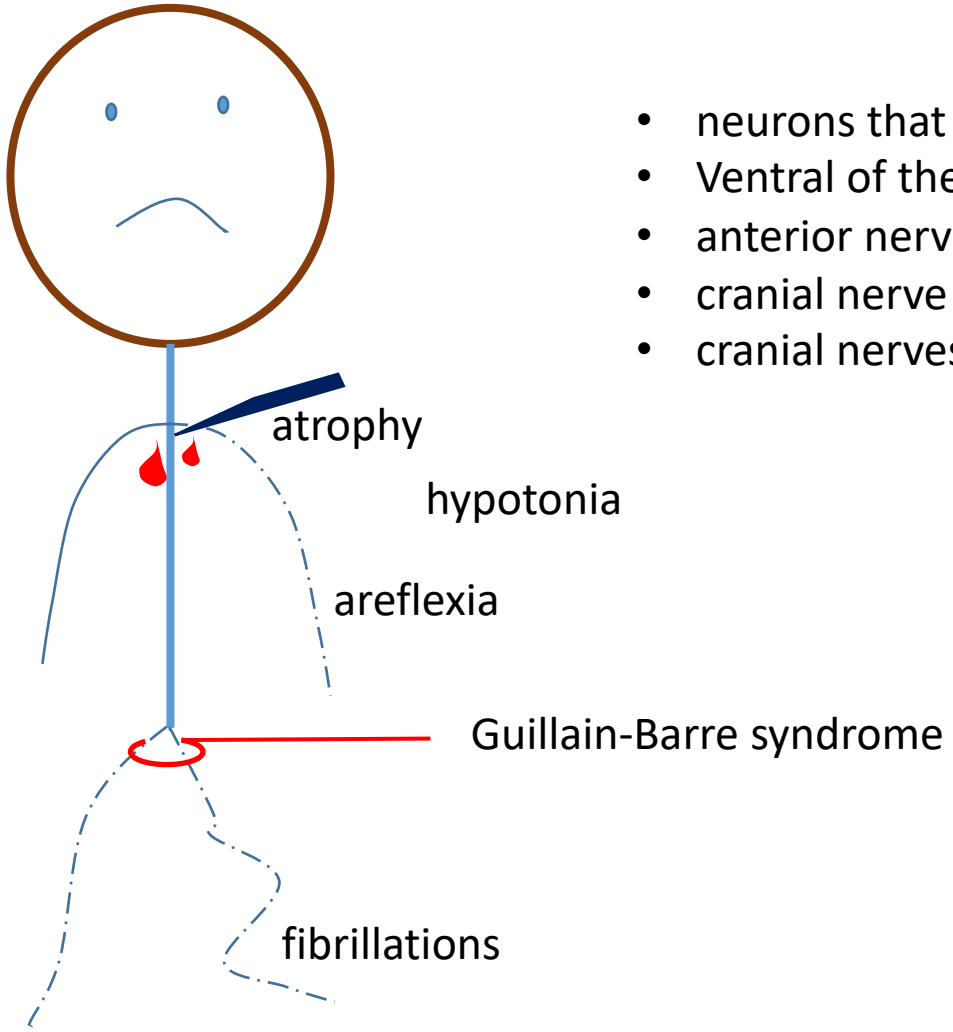
*Patients with a history of herpes simplex virus encephalitis in the previous weeks might have relapsing immune-mediated neurological symptoms (post-herpes simplex virus encephalitis). †Antibody testing should include testing of CSF. If only serum is available, confirmatory tests should be included (eg, live neurons or tissue immunohistochemistry, in addition to cell-based assay).

Upper Motor Neuron Disease

- Motor neurons start from the cortex or brain stem and go to the lower motor neurons. Injuries to this cause…
- Etiologies
  - Stroke
  - Trauma/HIE
  - Brain Neoplasm
  - CNS infections/abscesses
  - Myelopathy
  - Acute flaccid myelitis
- Causes decreased transmission of muscle contraction signals → weakness although muscle bulk can be normal
- Decreased regulation of lower motor neurons→ spasticity, hyperreflexia, +babinski

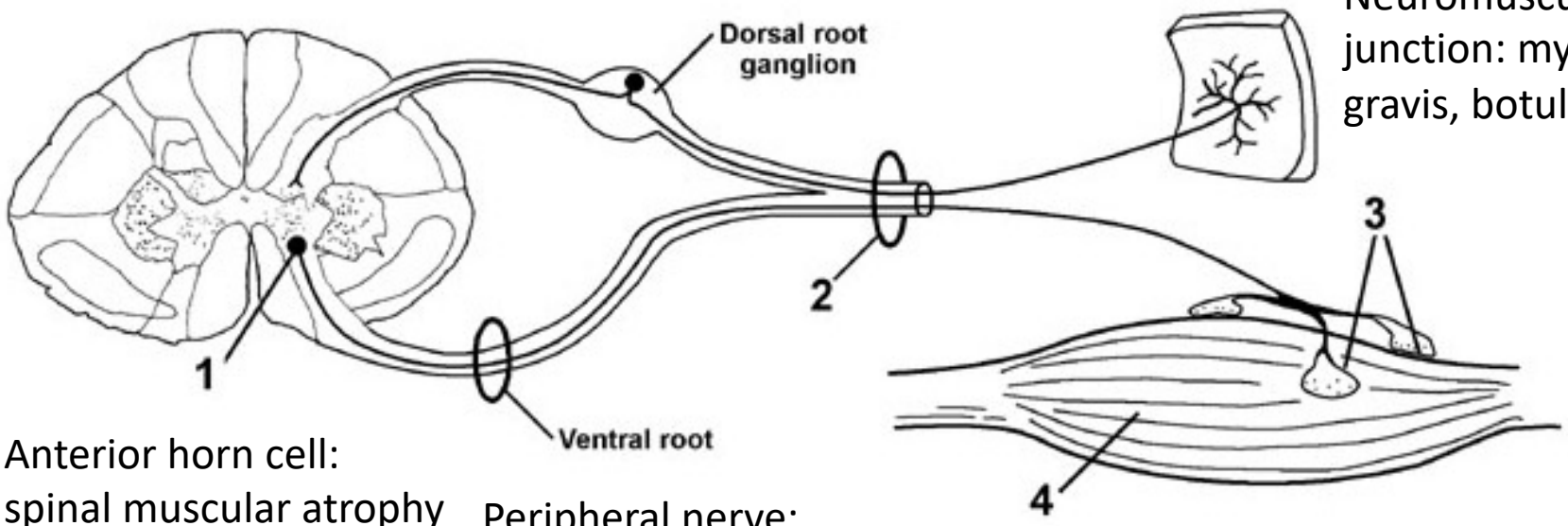


Lower Motor Neuron Disease



- neurons that innervate skeletal muscle
- Ventral of the spinal cord
- anterior nerve roots
- cranial nerve nuclei of the brainstem
- cranial nerves with motor function

Neuromuscular Disease: LMN Sites



Neuromuscular junction: myasthenia gravis, botulism

Anterior horn cell: spinal muscular atrophy (SMA), polio

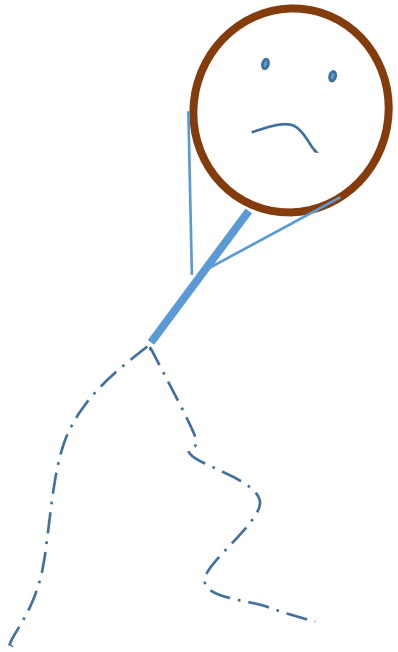
Peripheral nerve: neuropathies, GBS

Muscle fibers: muscular dystrophies, myositis

Spinal Muscular Atrophy

- Most common inherited disorder of spinal cord
- AR disorder → impaired programmed cell death in anterior horn cells and motor nuclei → hypotonia, weakness, and bulbar dysfunction
- 95% have mutation in SMN1 gene
- SMA 0 – severe neonatal form have arthrogryposis, weakness, mild facial weakness, respiratory failure
- SMA 1 (Werdnig Hoffman)- weakness within first 6mo, can be normal initially, facial expression normal, weakness worse proximally and in lower extremities, relative preservation of diaphragm

Guillain-Barre Syndrome



- Most common cause of acute flaccid paralysis in US
- Polyneuropathy with motor, sensory, dysautonomic features
- Immune response targets peripheral nerves

- Acute symmetric ascending weakness
  - 80% paresthesias
  - 80% lower back pain
  - 70% dysautonomia
- ~2 weeks of worsening → ~4 weeks plateau → recovery

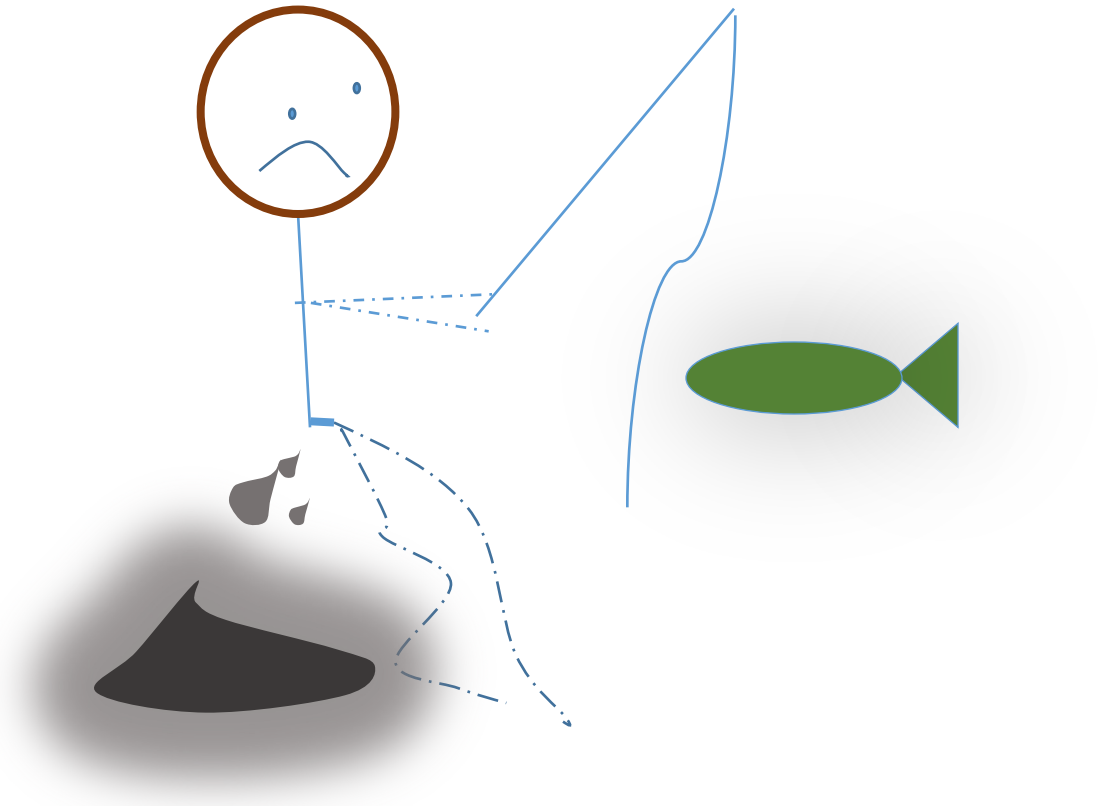
- NCS velocity <60%, prolonged/absent F waves = demyelination
- EMG fibrillations

- Rapid therapy: Plasmapheresis, IVIG

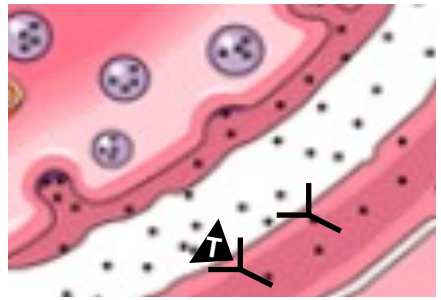
- Intubation indication (30%):
  - VC < 10-15mL/kg or < 1L
  - NIF < -20cm H_20
  - Loss of gag reflex
  - Rapidly worsening

Guillain-Barre Syndrome

- Miller-Fisher variant
  - ophthalmoplegia, ataxia, areflexia
  - Associated with *C. jejuni*



Myasthenia Gravis



- 85% have T-cells targeting postsynaptic acetylcholine receptor

- Weakness of voluntary muscles (including bulbar)

- CSF normal
- NCS show decrease in CMAP amplitudes with repetitive stimulation
- EMG normal

- Rapid therapy: plasmapheresis, IVIG
- Symptomatic therapy: pyridostigmine
- Chronic immunotherapy: prednisone, azathioprine, cyclosporine, rituximab…
- Surgical option: thymectomy

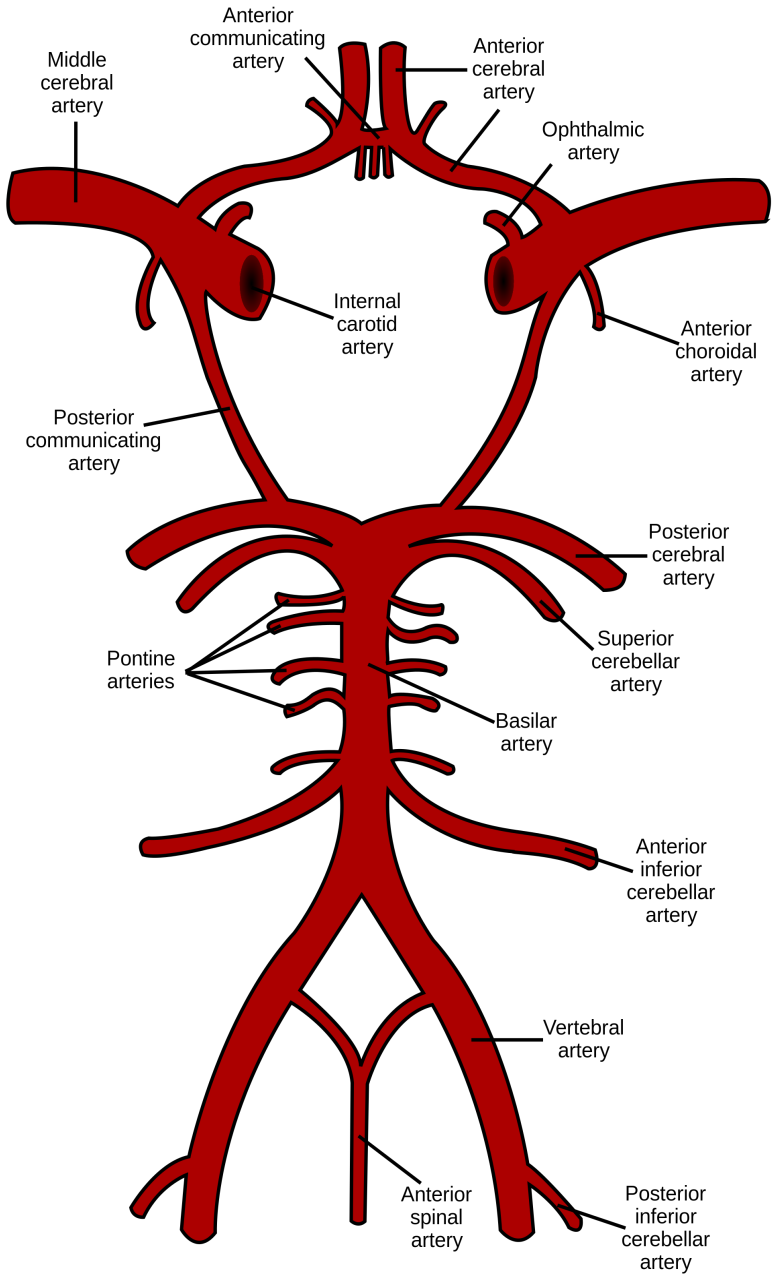
- Intubation indication:
  - VC < 10-15mL/kg or < 1L
  - NIF < -20cm H_20
  - Loss of gag reflex
  - Rapidly worsening

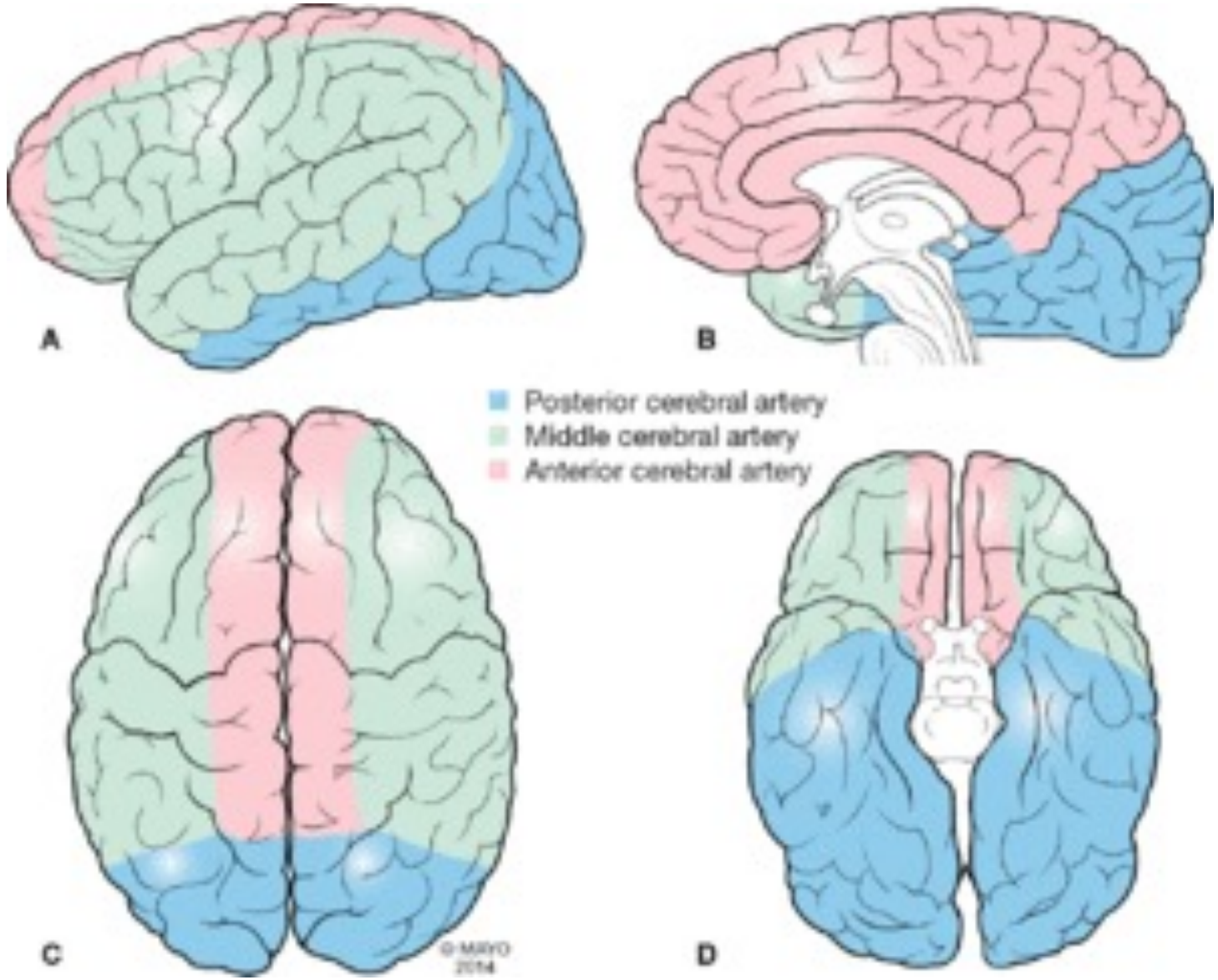
Pediatric Cerebrovascular Disease

- Stroke = brain damage that occurs as a result of blockage or breakage of blood vessels in brain
- Pediatric stroke care can vary significantly from adults
- Children can have significant delay in detection and care
- Overall goal is to initiate thrombolysis within 4.5hrs
- 3 primary types of strokes
  - Arterial Ischemic Stroke (AIS)
  - Cerebral Sinovenous Thrombosis (CSVT)
  - Hemorrhagic Stroke (HS)
- Important to differentiate between the 3 as treatment varies

Arterial Ischemic Stroke

- Most common form of stroke
- Carotid and vertebral arteries supply brain with oxygen.
- Connect in Circle of Willis
- MCA is most commonly affected




A
B
Posterior cerebral artery
Middle cerebral artery
Anterior cerebral artery
C
D
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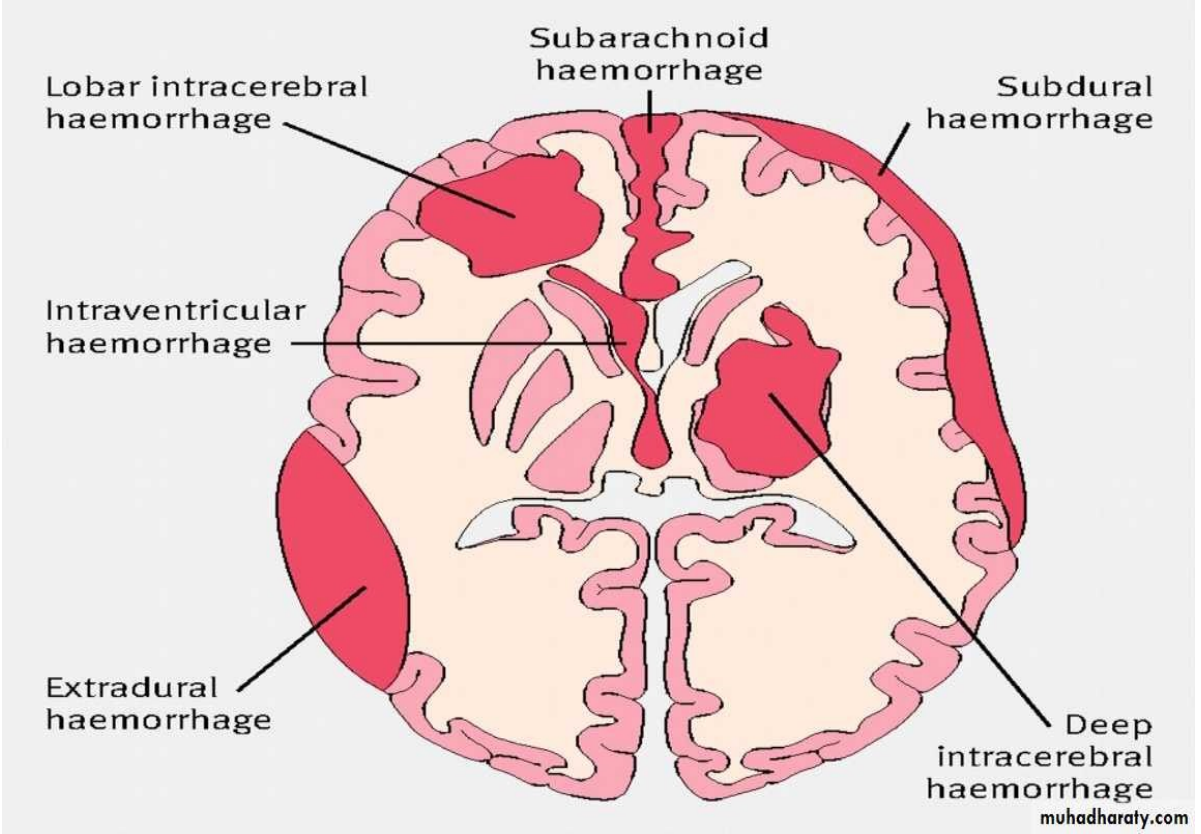
CSVT

- Abnormal clots form in veins or sinuses→ decreases drainage of blood→ decreased supply of blood → ischemic stroke
- Accounts for 25% of ischemic stroke
- Higher risk for secondary hemorrhage

Hemorrhagic stroke

- Determined by location of bleed
  - Intracerebral
  - Intraventricular
  - Subarachnoid
  - Subdural
  - Epidural



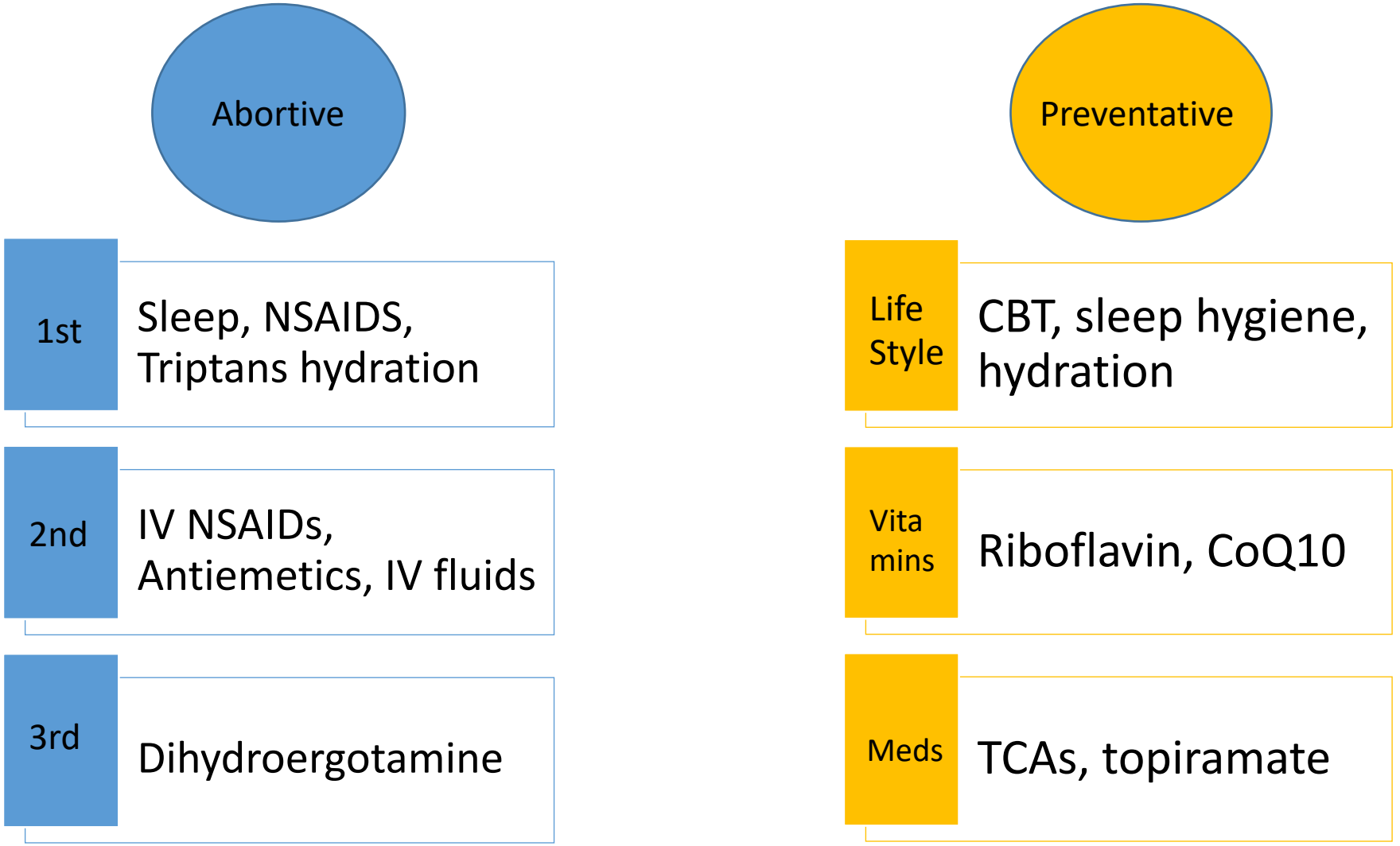
Presenting Signs and Symptoms

- International Pediatric Stroke Study (2011): 676 children p/w AIS
  - Hemiparesis (80%)
  - Speech disturbances (51%)
  - Altered consciousness (52%)
  - Headache (40%)
  - Seizures (31%)
- Children with CSVT p/w headache, seizures, lethargy, signs of increased ICP
- Children w/ HS p/w AMS, vomiting, headaches

Pediatric Headache

- <7yo → M>F, >7yo → F>M
- Primary HA syndromes
  - Migraine: 8-23% of adolescents
    - Headache attacks lasting 1-72hrs
    - Characteristics: mostly unilateral, pulsing, moderate or severe pain, aggravation of or causing avoidance of physical activity
    - N/V, photophobia/phonophobia
    - 10% will have associated auras
  - Tension Headache
    - Diffuse, non-throbbing, mild to moderate severity, and do not worsen with activity
    - 30 min to 7 days
  - Chronic Headache
    - Headache on 15 or more days per month with 8 having migraine features
    - Overall prevalence is 1.5%
- Concerning symptoms: progressive worsening, vomiting, waking from sleep, focal neurologic signs

Treatment of Pediatric Headaches



Delirium

- Occurs in up to 29% of critically ill patients
- 3 types based of psychomotor state but overall pts with irritability, mood lability, agitation, sleep/wake disturbance, and fluctuation of symptoms
  - Hyperactive
  - Hypomotor
  - Mixed
- Delusion and hallucinations are less common than adults
- Should screen for infections, medication effects, or autoimmune conditions
- Address volume and nutrition status and early mobilization
- Normalizing sleep/wake cycle and avoiding restraints
- Pharmacological aids are used when impeding care or concern for physical safety
- Atypical psychotics used more frequently

Somatic/Conversion Disorders

- Conversion disorder: physical symptom or deficit without an anatomical or physiological basis
  - F>M, 10-15yo
  - Risk factors: prior sexual abuse, preexisting psychiatric disease, domestic stress, unresolved grief, school difficulty, etc
  - Motor symptoms most common
- Somatic symptom disorder
  - Clues: vague medical hx, concerns not alleviated despite heavy utilization of care, frequent symptom checks
  - Diagnosis: Requires each of the following
    - 1 or more somatic symptom that causes stress or psychosocial impairment
    - Persistent thoughts or anxiety about symptoms with excessive time and energy devoted to them
    - Symptoms may change but disorder is permanent (>6mo)

ADHD

- Hyperactivity, impulsivity, and/or inattention that occur in more than one setting and affect function
- Treatment involves combination of
  - Behavioral interventions
  - Medication
    - Stimulants: amphetamines and methylphenidate
    - Non-stimulants: atomoxetine, clonidine, guanfacine
  - Psychologic interventions
  - School-based interventions

Autism

- Biologically based neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction and restricted, repetitive patterns of behavior, interests, and activities
- Genetic Testing: chromosomal microarray and fragile X
- MRI and EEG on case by case basis
- Treatment focuses on behavioral and educational interventions

Thanks for your attention!!
Any questions??

(and as always…Lets go Heat!!)