Little Brains, Big Questions

A Pediatric Neurology Update for Primary Care and Beyond

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Objectives

- Face to the name
- Variety of clinical topics pertinent to other clinicians
- Focus on low resource (relative for OR and SW WA) settings
- Open forum discussion

- Some resources potentially employable in clinical settings

Face to the name

Epic

Clinical Topics

- Autism & folinic acid
- Diagnosing epilepsy in primary care clinic
- Infantile epileptic spasms syndrome
- Syncope in primary care
- Subacute post-concussion care
- Neurology specific resources

Current Events – folinic acid & ASD

who has had this question in their office?

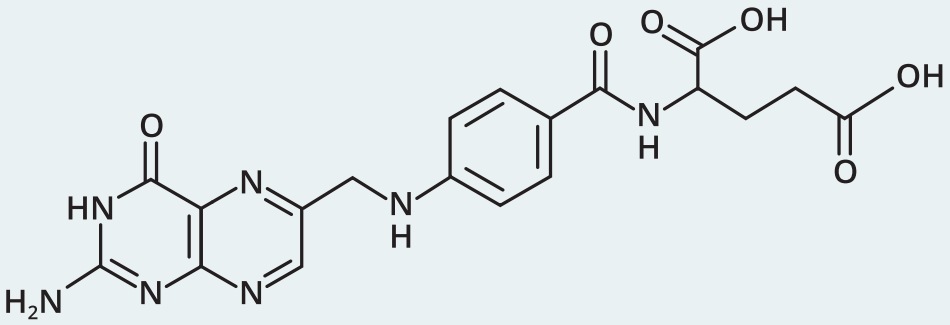
What are you saying in your clinic?

1. I’m not being asked
2. I think there is correlation, but unclear causation
3. I think there is clear causation
4. I do not see correlation or causation
5. I don’t know, let me refer you to _____

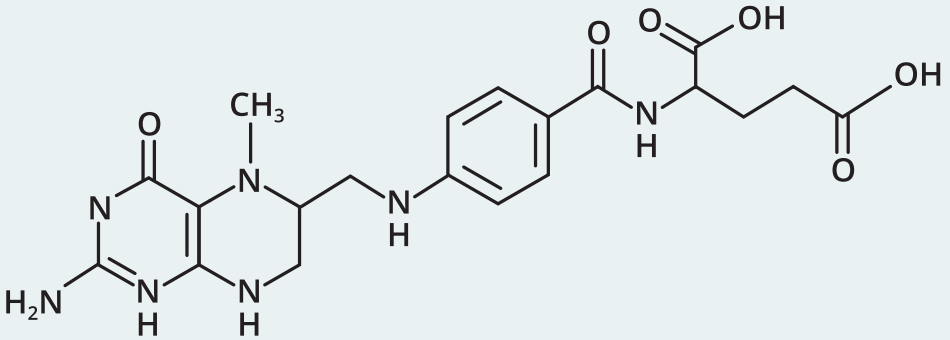
Cerebral folate deficiency

- Defined as systemic folate sufficiency, but CNS deficiency
- Chicken or egg?
    - Literature review shows a *very* heterogenous phenotype, typically co-occurring with radiographic evidence of acquired CNS damage, and *very* heterogenous methodologies with studies
- Proposed pathophysiologies
    - Folate transporter (FR1) autoantibodies
        - Epidemiological estimates ~10-15% in national population, but some cross-sectional studies suggest higher in ASD population
    - *FOLR1* mutation
    - Secondary metabolic disturbance to CNS injury / insult

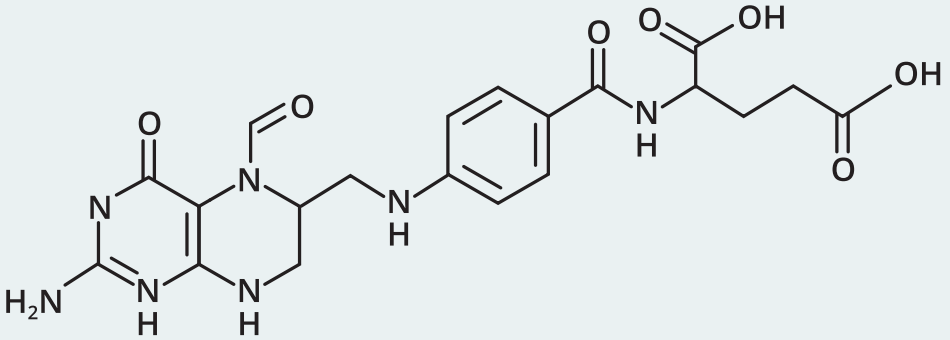
Figure 1. Chemical Structures



FOLIC ACID
$C_{19}H_{19}N_7O_6$

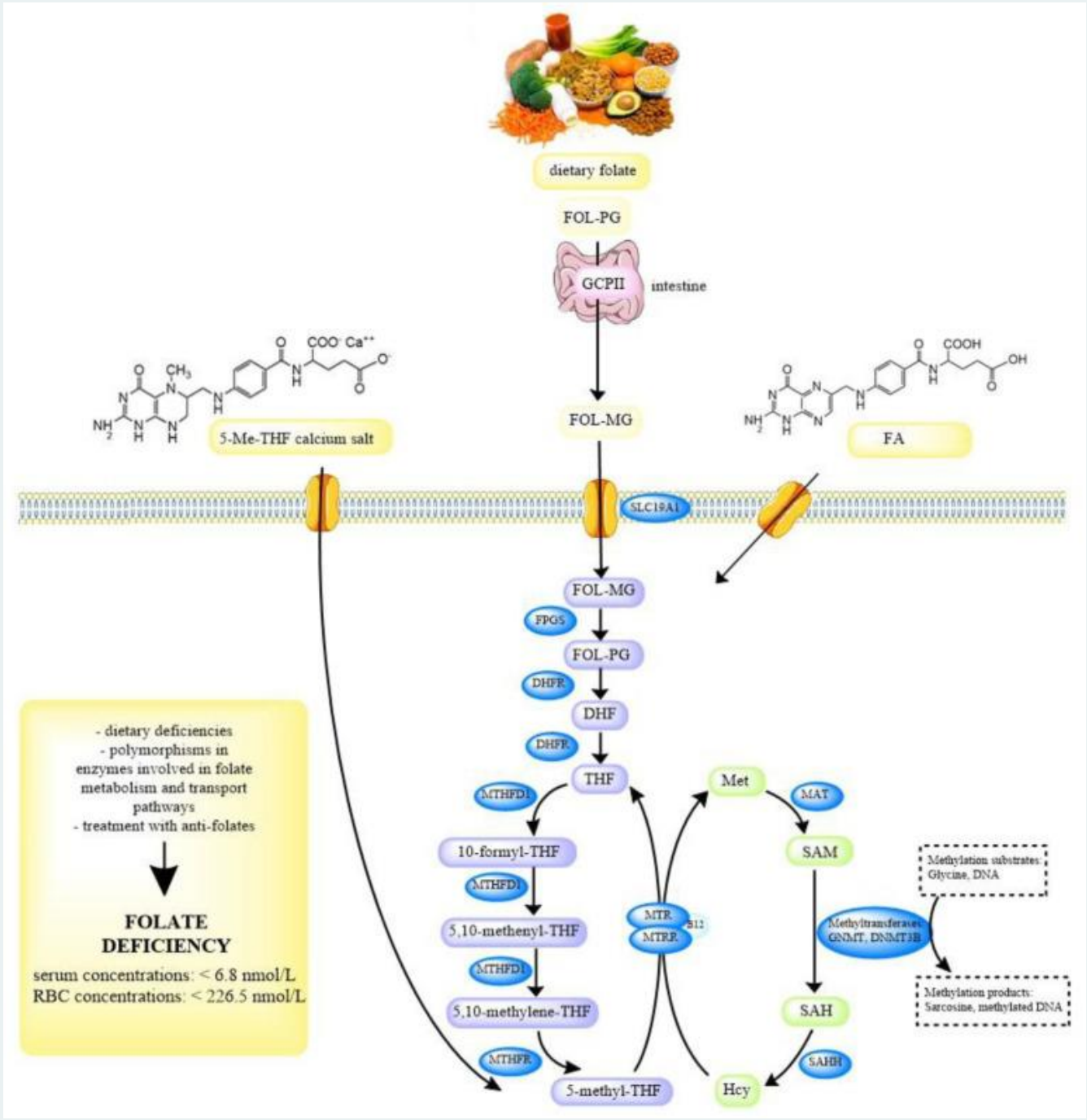


5-METHYLTETRAHYDROFOLATE
$C_{20}H_{25}N_7O_6$



FOLINIC ACID
$C_{20}H_{23}N_7O_7$

Oregon State's Micronutrient Information Center: https://lpi.oregonstate.edu/mic/vitamins/folate



Vidmar Golja M, et al. Folate Insufficiency Due to MTHFR Deficiency Is Bypassed by 5-Methyltetrahydrofolate. J Clin Med. 2020 Sep 2;9(9):2836. doi: 10.3390/jcm9092836. PMID: 32887268.

The latest hot topic:
ASD, CFD and folinic acid

- In an early case series of 28 children, 4 had ASD.
  - The proposed clinical spectrum has expanded since with subsequent case series
- Importantly, note the frequency of comorbid signs / symptoms
- Treatment with folinic acid (Leucovorin or Isovorin) 0.5-2 mg/kg/day
  - ADEs: worsening aggression, insomnia, GERD, ?worsening hyperactivity

Ramaekers VT, Rothenberg SP, Sequeira JM, Opladen T, Blau N, Quadros EV, Selhub J. Autoantibodies to folate receptors in the cerebral folate deficiency syndrome. N Engl J Med. 2005 May 12;352(19):1985-91. doi: 10.1056/NEJMoa043160. PMID: 15888699.

Table 1. Clinical Characteristics of Patients with Cerebral Folate Deficiency, before and after Folinic Acid Treatment.*

Characteristic	Patient No.																											Rate of Improvement in Symptoms
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	*% of subjects*
Sex	M	M	F	F	M	M	F	M	M	F	M	F	M	M	M	M	M	M	M	M	F	M	M	F	F	M	M	M	
Age at diagnosis (yr)	1.5	1.5	2.2	2.2	2.5	2.5	2.5	2.7	3.2	3.5	3.5	3.5	4.7	4	5	5	5	5.2	5.3	6	6.5	6.5	7.5	8.7	11	12	15	16	
Irritability, marked unrest, sleep disturbances	+/–	+/–	+/–	+/–	–	+/–	+/–	–	+/–	+/–	+/–	+/–	–	+/+	+/–	+/+	+/–	+/+	+/–	+/–	+/–	–	+/–	–	+/–	+/+	–	–	81
Head-growth deceleration after 6 mo	+/–	+/–	–	+/–	+/–	+/–	–	+/–	–	–	–	+/–	+/–	+/–	+/–	+/–	–	+/+	+/–	–	+/–	+/–	–	–	+/–	+/+	+/+	+/–	84
Psychomotor retardation	+/–	+/+	+/–	+/+	+/+	+/–	+/–	+/–	+/–	+/+	+/–	+/+	+/+	+/+	+/+	+/+	+/–	+/+	+/+	+/–	+/+	+/–	+/–	+/+	+/+	+/+	+/+	+/+	39
Frank autistic features and late infantile autism†	–	–	–	+/–	–	–	–	–	+/–	–	–	–	–	–	–	+/+	–	–	+/+	–	–	–	–	–	–	+/+	–	–	40
Cerebellar ataxia																													85
Wobbly gait, difficulty walking	–	–	–	–	+/–	–	–	0/+	–	–	0/+	–	–	–	+/–	–	+/–	–	+/–	+/–	–	–	–	–	–	–	–	–	
Ataxia with frequent falls	+/–	+/–	+/–	–	–	+/+	+/–	+/–	–	–	–	–	+/–	–	–	–	–	–	–	–	+/–	+/–	+/–	+/–	–	0/+	+/–	+/–	
Severe ataxia	–	–	–	+/–	–	–	–	–	+/–	+/–	+/–	+/+	–	+/–	–	–	–	+/+	–	–	–	–	–	–	+/+	+/–	–	–	
Pyramidal tract signs in legs	+/–	–	+/–	+/–	+/+	+/–	–	+/–	+/–	–	+/–	+/+	+/–	–	–	+/–	–	+/–	+/–	–	–	–	–	–	+/+	–	+/–	+/–	81
Dyskinesias (e.g., choreoathetosis and ballismus)	–	–	–	–	–	–	–	–	–	–	–	+/+	–	+/+	–	+/–	–	+/+	+/–	–	–	–	–	–	+/+	–	–	–	33
Occasional seizures†	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+/–	–	–	–	–	+/–	–	–	–	100
Epilepsy	+/–	–	–	+/–	–	–	–	–	–	+/–	–	+/–	–	–	–	–	–	+/–	–	–	–	–	–	+/–	–	–	–	–	100
Ocular strabismus†	–	–	–	–	–	–	–	–	–	–	–	+/+	+/+	–	–	–	–	+/+	–	–	–	–	–	–	+/–	–	+/+	+/–	33
Visual failure or optic atrophy†	–	–	–	–	–	–	–	–	–	–	–	–	+/+	–	–	–	–	–	–	–	–	–	–	–	+/+	–	–	–	0
Sensorineural hearing loss†	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+/+	–	+/+	0

* +/– denotes improvement with treatment, +/+ no improvement with treatment, – symptoms not present, and 0/+ decreased severity after treatment.
† This characteristic is a less common feature of cerebral folate deficiency.

Ramaekers VT, Rothenberg SP, Sequeira JM, Opladen T, Blau N, Quadros EV, Selhub J. Autoantibodies to folate receptors in the cerebral folate deficiency syndrome. N Engl J Med. 2005 May 12;352(19):1985-91. doi: 10.1056/NEJMoa043160. PMID: 15888699.

Subsequent studies

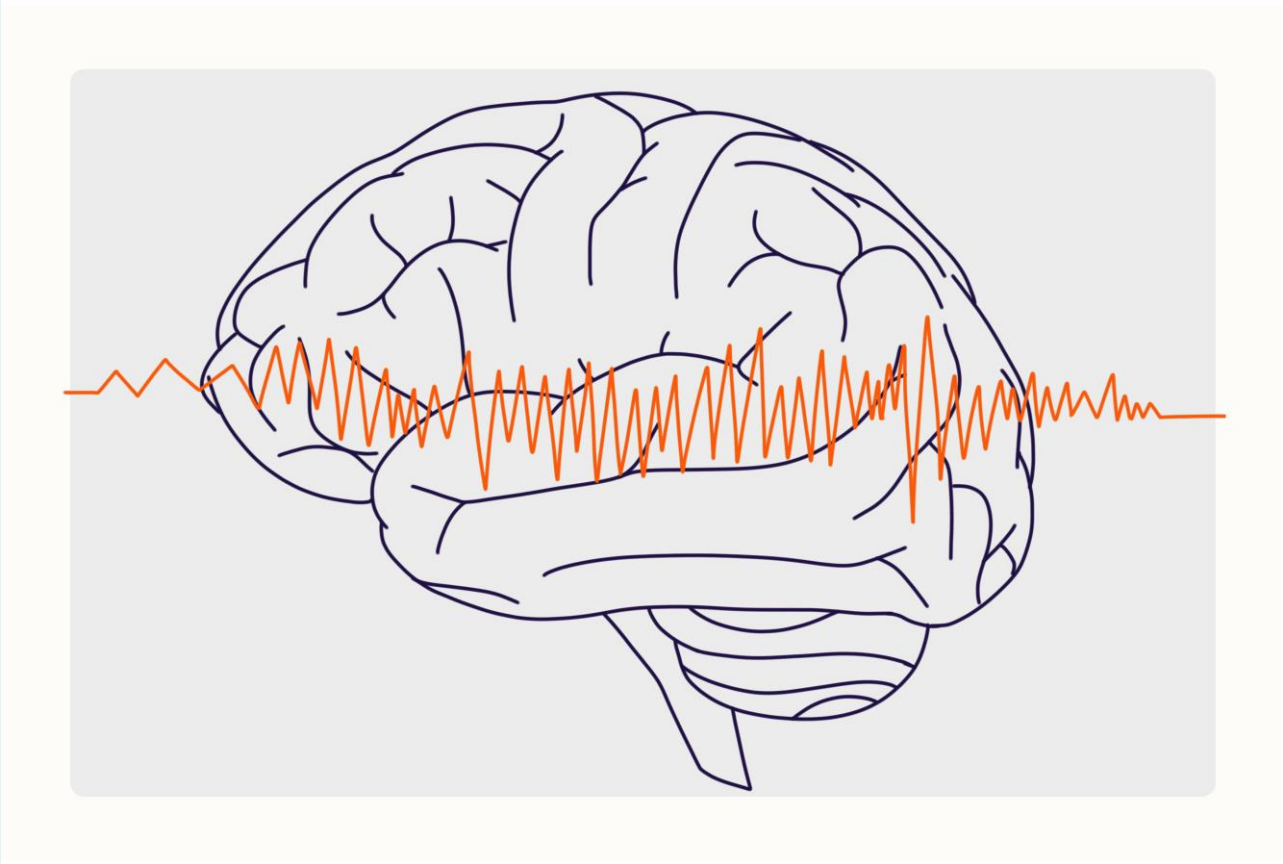
- Widely variable in methodology, intervention, blinding, and result gathering
- Do we check CSF folate? Antibodies? Serum only or also CSF antibodies?
    - Do we trend? Conversion rate?
- Do we blind parents? What is the study population?
- What do we use as measures? Parent report? Developmental assessments?

The TL;DR

- Methodological inquisitiveness
- Recognizable narrow phenotype.
  - But how inclusive should definition be?
- Unclear sensitivity / specificity of testing results
- Relatively low risk supplement options
- Ethical questions and implications
- AAP, SDBP, CNS statement easy tipsheet

Diagnosing epilepsy in primary clinic

What is the ILAE definition of epilepsy?



What is the ILAE definition of epilepsy?

- Epilepsy is any of the following:
  - ≥ 2 unprovoked (or reflex) seizures occurring ≥24 hours apart
  - 1 unprovoked (or reflex) seizure and a probability of recurrence ≥60% in the next 10 years
  - Diagnosis of an epilepsy syndrome
- Note, recurrence risk after 2 unprovoked seizures = ~60%

- Epilepsy is considered to be resolved for individuals who had an age-dependent self-limited epilepsy syndrome but who are now past the applicable age (e.g. CAE), or for those who have remained seizure-free for the last 10 years, with no seizure medication for the last 5 years.

So, with that definition, what can you do to evaluate for underlying epilepsy?

History and Plan

Focused question taking to elicit common epilepsy syndromes:

- CAE
- JME
- SeLECTS
- Focal

Jandhyala N, et al. Unrecognized Focal Nonmotor Seizures in Adolescents Presenting to Emergency Departments. Neurology. 2024 May;102(10):e209389. doi: 10.1212/WNL.0000000000209389. Epub 2024 May 1. PMID: 38691824; PMCID: PMC11404317.

History and Plan

Focused question taking to elicit common epilepsy syndromes:

- CAE
- JME
- SeLECTS
- Focal

- Interruptible?
  - If not, what has been done to interrupt?
- Frequency (CAE vs JAE)
- Duration (CAE vs JAE)
- Declining school performance
- Hyperventilate in office (CAE)

Jandhyala N, et al. Unrecognized Focal Nonmotor Seizures in Adolescents Presenting to Emergency Departments. Neurology. 2024 May;102(10):e209389. doi: 10.1212/WNL.0000000000209389. Epub 2024 May 1. PMID: 38691824; PMCID: PMC11404317.

History and Plan

Focused question taking to elicit common epilepsy syndromes:

- CAE
- JME
- SeLECTS
- Focal

- Will likely be in office for GTCs, not myoclonic jerks
- Myoclonic jerks in ~100%
  - Particularly in AM
  - ?Clumsiness?
  - Preserved consciousness, despite generalized!
- +/- Comorbid GTCs, absence
- Triggers: sleep deprivation, EtOH, ± photic

Jandhyala N, et al. Unrecognized Focal Nonmotor Seizures in Adolescents Presenting to Emergency Departments. Neurology. 2024 May;102(10):e209389. doi: 10.1212/WNL.0000000000209389. Epub 2024 May 1. PMID: 38691824; PMCID: PMC11404317.

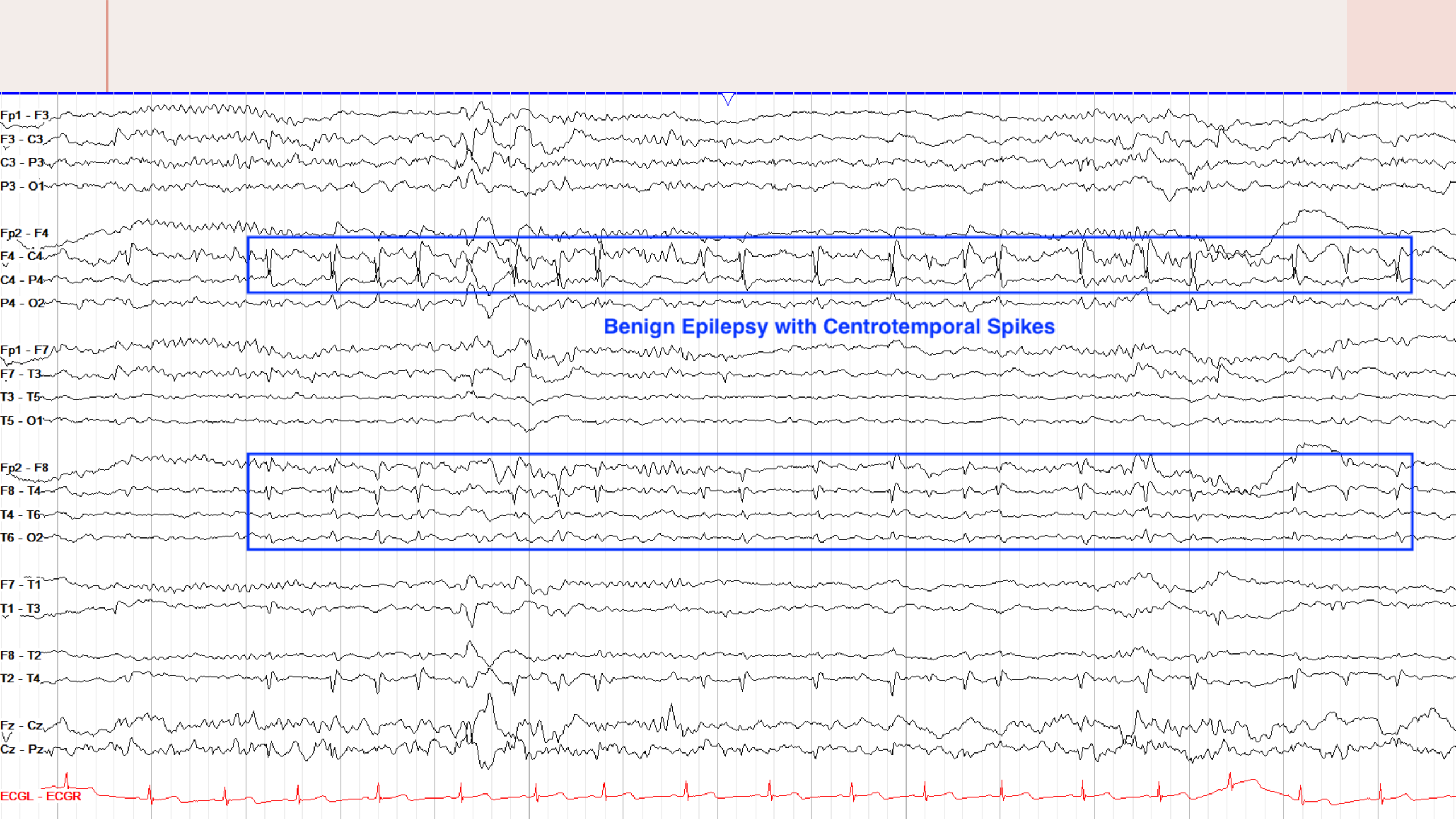
History and Plan

Focused question taking to elicit common epilepsy syndromes:

- CAE
- JME
- SeLECTS (formerly BECTS, Rolandic)
- Focal

- Attention to changes in language, executive functioning
- ¾ are nocturnal seizures or upon awakening
- Semiology brief bulbar and hemifacial sensorimotor seizures that can evolve to focal or GTCs

Jandhyala N, et al. Unrecognized Focal Nonmotor Seizures in Adolescents Presenting to Emergency Departments. Neurology. 2024 May;102(10):e209389. doi: 10.1212/WNL.0000000000209389. Epub 2024 May 1. PMID: 38691824; PMCID: PMC11404317.


Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Benign Epilepsy with Centrotemporal Spikes
Fp1 - F7
F7 - T3
T3 - T5
T5 - O1
Fp2 - F8
F8 - T4
T4 - T6
T6 - O2
F7 - T1
T1 - T3
F8 - T2
T2 - T4
Fz - Cz
Cz - Pz
ECGL - ECGR

History and Plan

Focused question taking to elicit common epilepsy syndromes:

- CAE
- JME
- SeLECTS
- Focal

- After first motor seizure:
  - Did you feel anything at the beginning of the seizure? If so, have you ever felt the same thing before?
  - Before today, did you have any feelings (such as feeling scared, anxious, or worried, a sudden thought out of nowhere, a "deja vu") that come on suddenly for no reason and last less than 5 minutes?
- 5 key characteristics suggestive of seizures: sudden-onset, short-lasting, strange or difficult-to-describe, stereotyped, and postictal symptoms

Jandhyala N, et al. Unrecognized Focal Nonmotor Seizures in Adolescents Presenting to Emergency Departments. Neurology. 2024 May;102(10):e209389. doi: 10.1212/WNL.0000000000209389. Epub 2024 May 1. PMID: 38691824; PMCID: PMC11404317.

History and Plan

Focused question taking to elicit common epilepsy syndromes:

- CAE
- JME
- SeLECTS
- Focal

The Pediatric Neurology Holy Trinity:

- EEG (with sleep if possible)
- MRI (epilepsy protocol if you have it)
- Genetics

Jandhyala N, et al. Unrecognized Focal Nonmotor Seizures in Adolescents Presenting to Emergency Departments. Neurology. 2024 May;102(10):e209389. doi: 10.1212/WNL.0000000000209389. Epub 2024 May 1. PMID: 38691824; PMCID: PMC11404317.

Levetiracetam for the generalist

Why do we love it?

- Pharmacokinetics
- Long term tolerability
- Unique MOA
- Familiarity
- Does not worsen any epilepsy syndromes (except in case reports)
- "Clean" – ok with OCPs or other Rx

Practical considerations:

- Starting dose 20-30 mg/kg/day divided BID or 500-750mg BID, whichever is less.
- No uptitration required, but possible
- MC adverse effects include irritability, ataxia, drowsiness.
  - Typically improve within 2-4 weeks
- PK similar for liquid, pill, IV

Infantile epileptic spasms syndrome (IESS)

with focus on presentation and prognosis

IESS

Basics

- Natural history
- Video review

Timeline of importance – emergency or urgency?

- First episode a few days ago
- First episode 4 weeks ago, increasing frequency, clustering, etc

Inequities

1. InfantileSpasms.Org
2. O'Callaghan FJ et al. The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study. Epilepsia. 2011 Jul;52(7):1359-64. doi: 10.1111/j.1528-1167.2011.03127.x. Epub 2011 Jun 10. PMID: 21668442.
3. Baumer FM, et al; National Infantile Spasms Consortium. Inequities in Therapy for Infantile Spasms: A Call to Action. Ann Neurol. 2022 Jul;92(1):32-44. doi: 10.1002/ana.26363. Epub 2022 Apr 28. PMID: 35388521; PMCID: PMC9482145.
4. Abath CB, et al. Delays to care in infantile epileptic spasms syndrome: Racial and ethnic inequities. Epilepsia. 2024 Jan;65(1):107-114. doi: 10.1111/epi.17827. Epub 2023 Dec 7. PMID: 37953072.

IESS
Treatment and Prognosis

Still variable by institution, but basic choice is hormonal vs non-hormonal

- Hormonal = ACTH or prednisone
- Non-hormonal = vigabatrin (Sabril)

If comorbid tuberous sclerosis → vigabatrin always

PCP ADRs to consider: hypertension, infection. VGB specific peripheral vision loss, MRI changes

Other ASMs?

Etiological dependent

- Normal MRI, genetic testing, PMHx? → more optimism

Timing of treatment dependent

- Where urgency vs emergency comes in
- Studies most often look at 30d from first clinical spasm

Effect of first line treatment dependent

Syncope in primary care

Considerations from your friendly neighborhood neurologist
(with a spooky case)

Skipping the basics on this one

First, the most common reason for syncope to end up in neurology clinic

Second, a case

Syncopal convulsions

- Commonly brief, <20s
- Preceded by syncope.
  - Thought to be anoxic reflex? ?brainstem release phenomena?
- Typically less rhythmic than epileptic seizure
- Can be subtle
  - More commonly noticed by health professionals than common bystanders
- EEGs usually demonstrate generalized slowing followed by high-voltage frontal delta activity

A case break

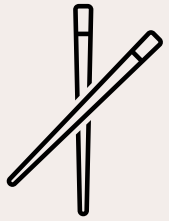
- 14y M with subacute onset and worsening of orthostatic intolerance leading to recurrent episodes of transient loss of consciousness.
  - There was generalized clonic activity with first two events, but preceded by pre-syncope prodrome.
- Hx of ADHD, OCD, EoE, adrenal insufficiency 2/2 steroids (resolved)
- Sister with POTS, migraines
- ED presentation after one episode

Serial physical exams

8/27/24: normal

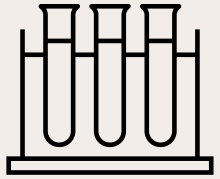
8/21/24: normal

Best next step?

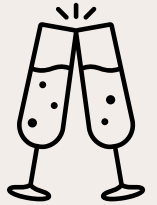


EMG

TINCTURE OF TIME



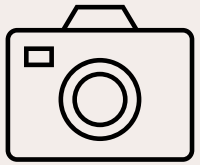
SERUM LABS



LUMBAR PUNCTURE

CONSULTS

DIVE INTO TREATMENT



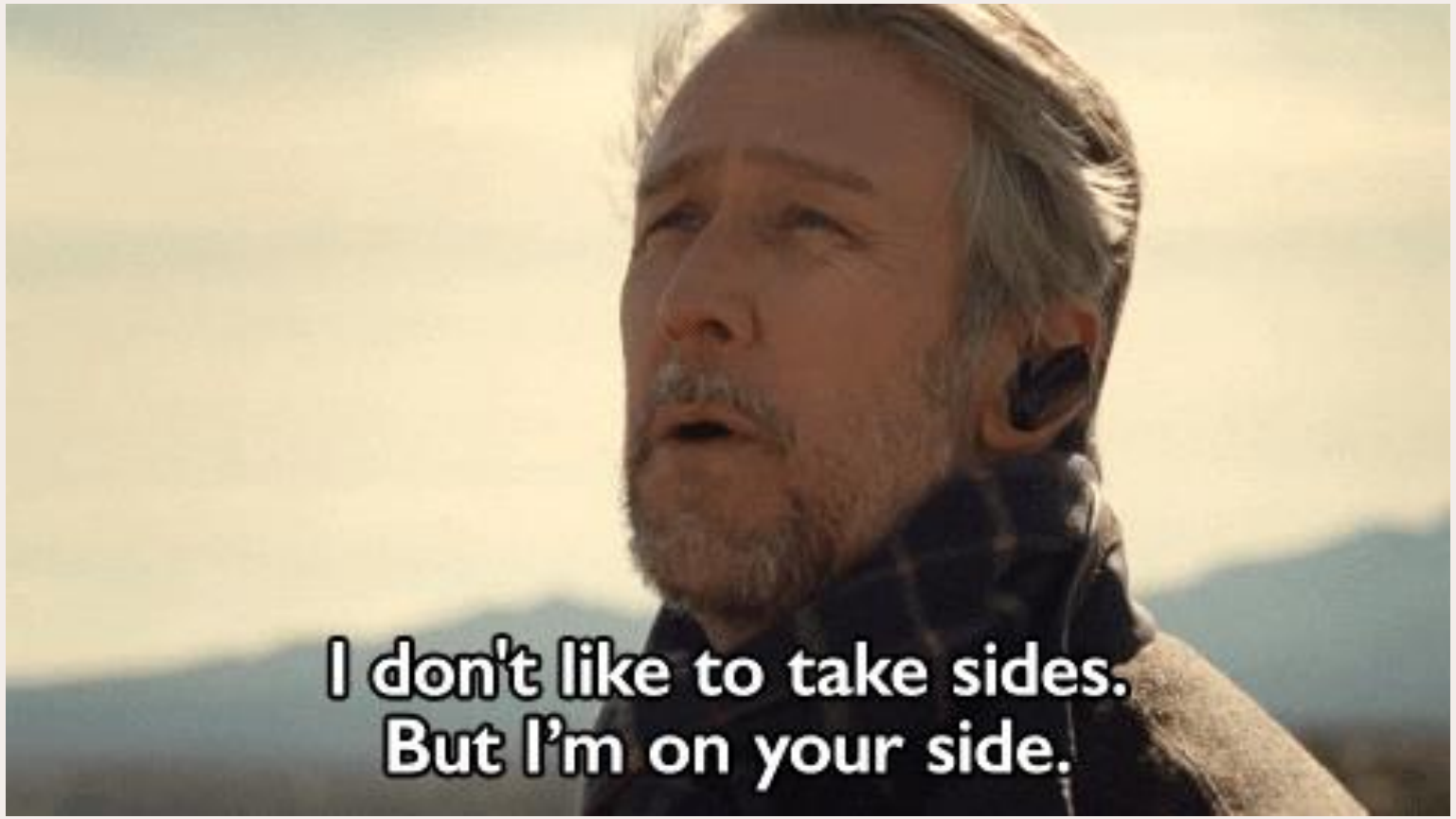
Imaging

EEG

EMG

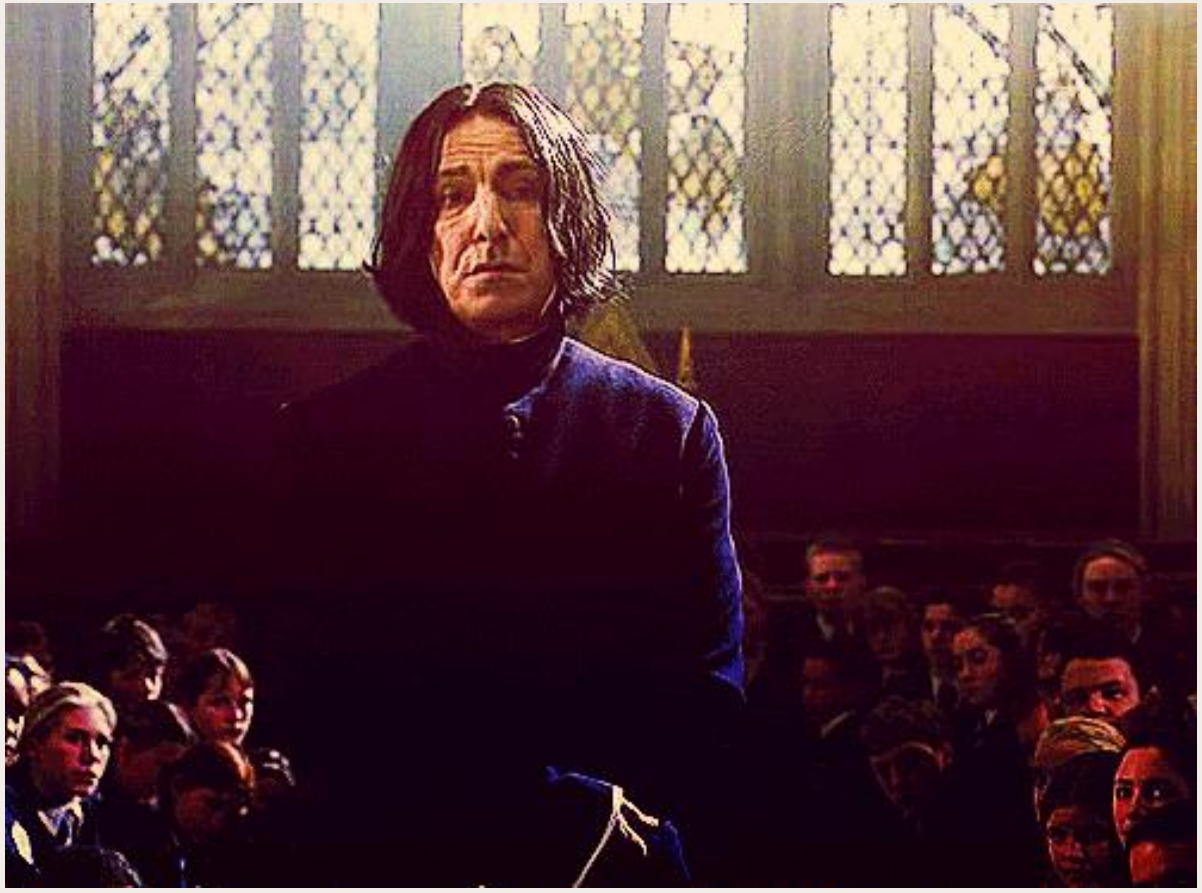
Tincture of time

A worthwhile option given exam and typical causes.



Serum Labs

- Normal CBC, CMP, UA, cortisol, UDS



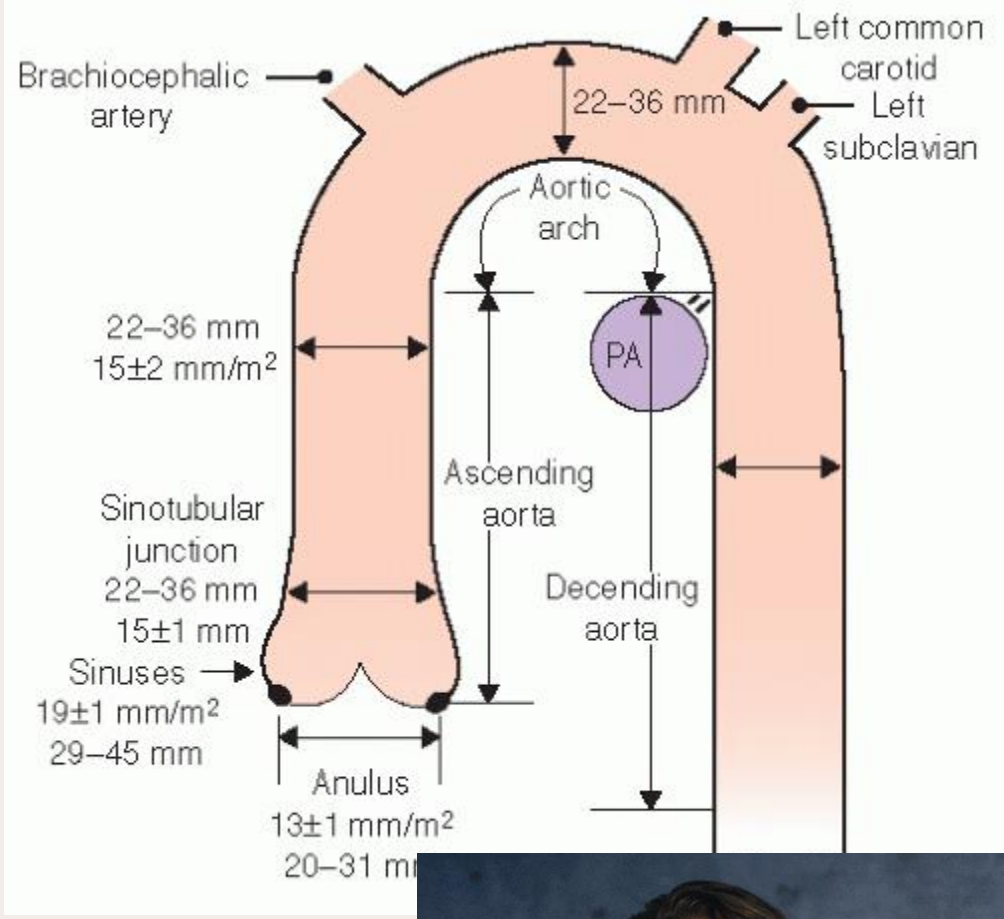
Lumbar puncture

Consults

Cardiology

- EKG NSR
- Echo with tiny coronary to pulmonary artery fistula and mildly dilated sinotubular junction (thought not hemodynamically significant)
- Event patch for home
- No further IP workup

Event patch result was: Rare PACs/PVCs. Otherwise sinus rhythm, including triggered events/symptoms. Normal monitor for age.



Treatment

- Did encourage hydration, increased salt intake.
- No cardiac meds, ASMs.

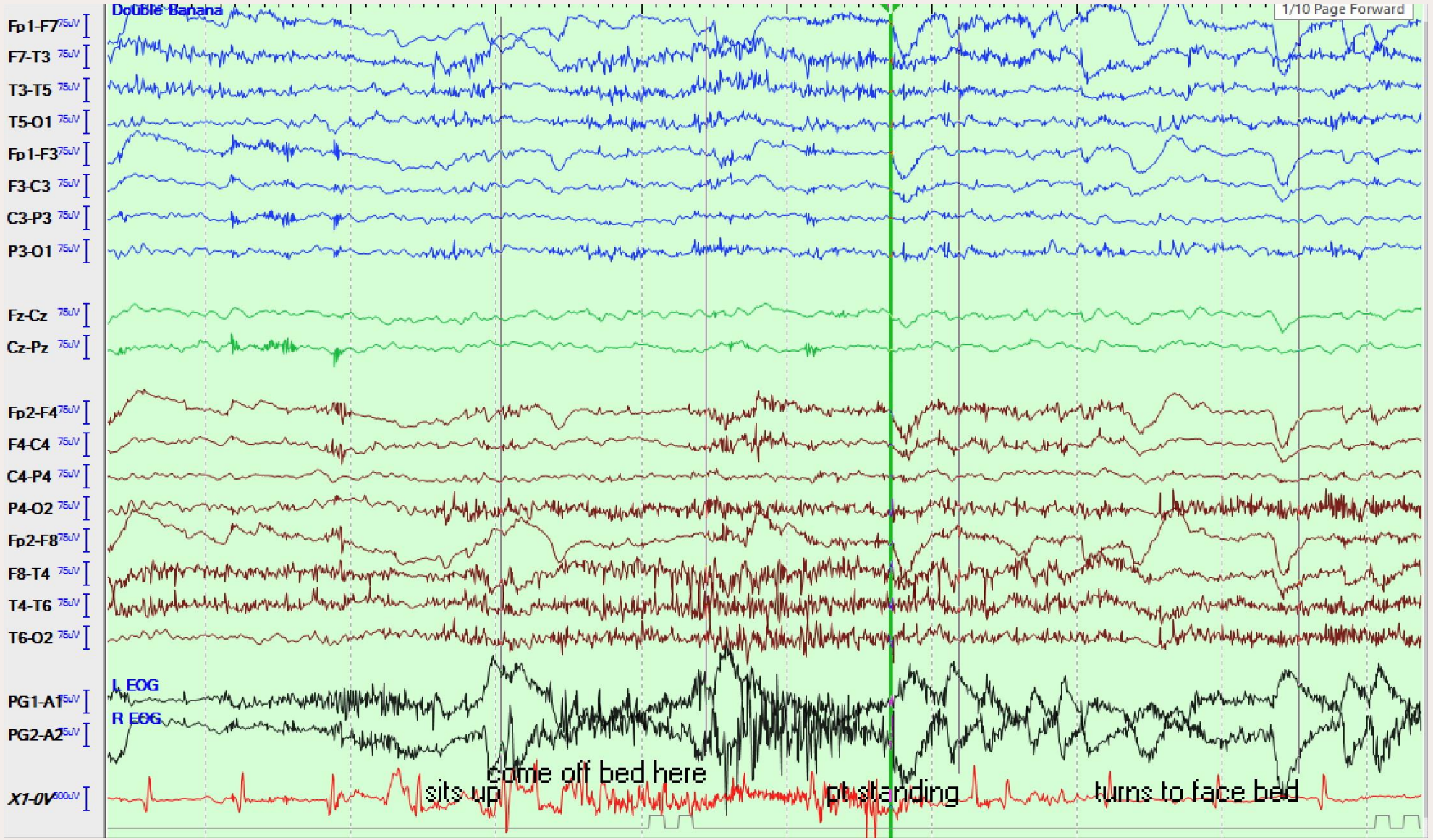
Imaging

- CTH obtained with first ED presentation. Read as normal

EEG

- 8/19/24 routine: normal awake and asleep
- 8/28/24 video IP: One episode of probable syncope was recorded, in which the patient stood up, collapsed to the bed with the emergence of high voltage slowing, then recovered himself within seconds. A second episode of feeling woozy upon arising did not lead to collapse or EEG slowing. Interictal EEG is normal, as it was in the outpatient clinic.

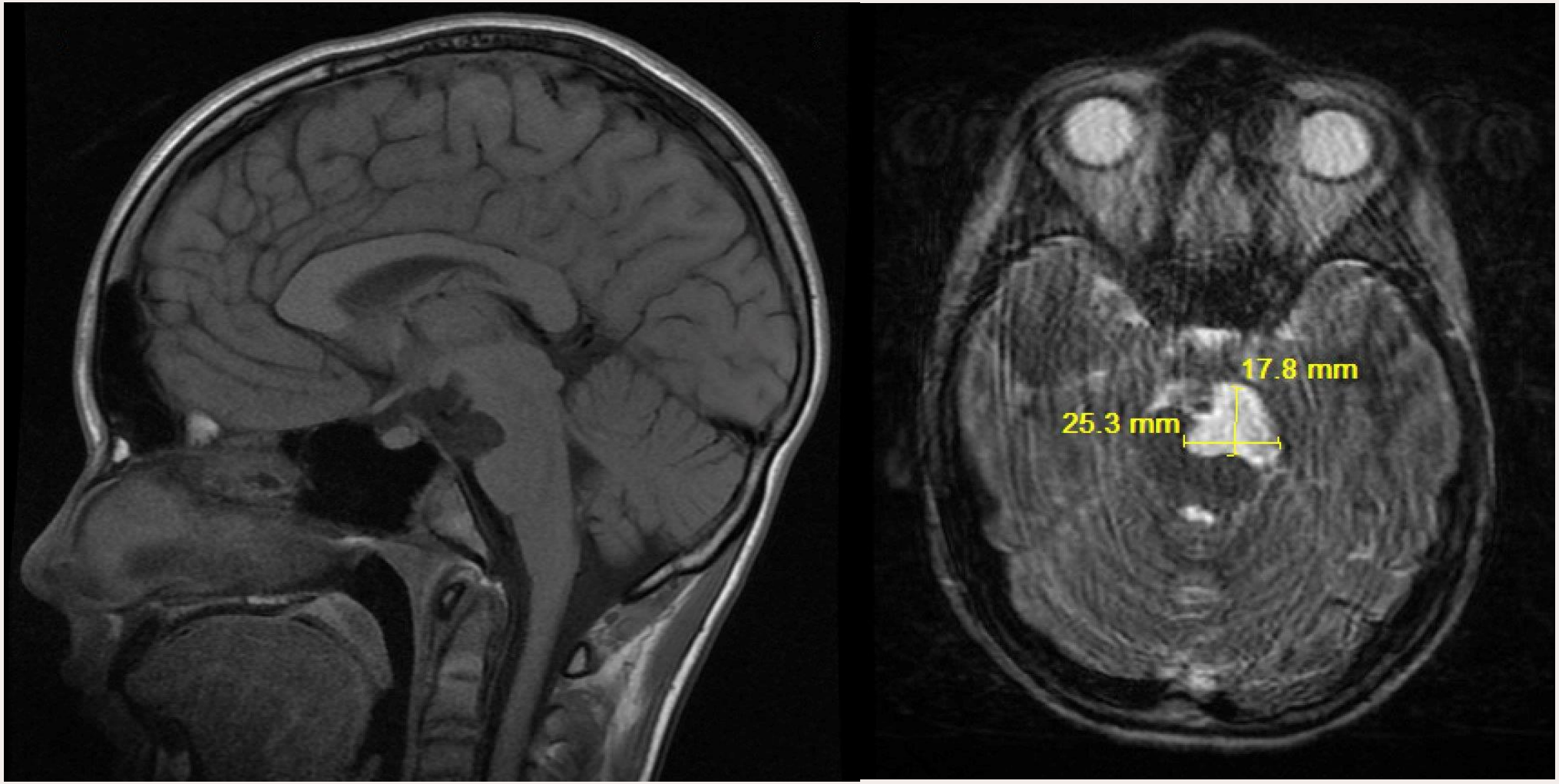
EEG


Double Banana
1/10 Page Forward
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp1-F3
F3-C3
C3-P3
P3-O1
Fz-Cz
Cz-Pz
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
PG1-A1
PG2-A2
L EOG
R EOG
X1-0V
sits up
come off bed here
pt standing
turns to face bed

Patient discharged from IP service

…but episodes recurred, and continued to increase in frequency

9/3/24 MRI brain wwo contrast



Cognitive biases takeaways

- Anchoring
  - HCT read as normal (but was not)
  - EEG c/w orthostatic syncope
- Overconfidence
  - In reviewing CTH, in taking history, etc.
- Framing effect
  - History = strong orthostatic component
- Premature closure
  - EEG and history allowed for some presumption of a diagnosis already being found

Learning points in regards to syncope

- The general recommendations from numerous expert panels and groups are to abstain from further workup in "simple syncope"
- But what is "simple"?
- In this case, the history is what prompted continued workup beyond EEG

Red flags:

- Rapidly progressive in frequency*
- Focal neurological deficits
- Additional new onset / concurrent onset cardiac or neurological complaints
- Delayed return to baseline after return of consciousness, or prolonged duration of LOC

Subacute post concussion care

Basics

- Est 42m per year globally
- Pathophysiology theories
- Epidemiology: mostly adolescents and young adults, M>F
    - Access to care follows typical socioeconomic and racial disparities
- Definition proposed[1]
- Conflicting reports on chronicity

1. Cassidy JD, et al. Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med. 2004 Feb;(43 Suppl):28-60. doi: 10.1080/16501960410023732. PMID: 15083870.

(selected) Morbidity after mTBI

- Sleep
- Headache
- Activity intolerance

Sleep

- A pre-existing issue in our patient population
- Post mTBI issues:[1]
  - Reduced total sleep time
  - Sleep fragmentation
  - Deterioration in overall quality

Treatment!

- CBIT is first line
- Melatonin consideration[2-4]
- Theoretical: Avoid GABA-ergic medications given possible impaired neural recovery

1. Montgomery MC, Baylan S, Gardani M. Prevalence of insomnia and insomnia symptoms following mild-traumatic brain injury: A systematic review and meta-analysis. Sleep Med Rev. 2022 Feb;61:101563. doi: 10.1016/j.smrv.2021.101563. Epub 2021 Nov 2. PMID: 35033968.
2. Grima NA, et al. Efficacy of melatonin for sleep disturbance following traumatic brain injury: a randomised controlled trial. BMC Med. 2018 Jan 19;16(1):8. doi: 10.1186/s12916-017-0995-1. PMID: 29347988; PMCID: PMC5774131.
3. Barlow KM, et al. Efficacy of Melatonin in Children With Postconcussive Symptoms: A Randomized Clinical Trial. Pediatrics. 2020 Apr;145(4):e20192812. doi: 10.1542/peds.2019-2812. Epub 2020 Mar 26. PMID: 32217739.
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Headache

Most common reported physical symptom after mTBI[1,3]

Those with chronic HA more likely to experience depression

↑ HA scores have been correlated with
↑ scores in all domains of SCAT survey[2]

Treatment!

- Early riboflavin (200-400mg)[2,4]
- Why not add in Magnesium and coenzyme Q10?
- Addressing lifestyle factors e.g. sleep, mood, etc.

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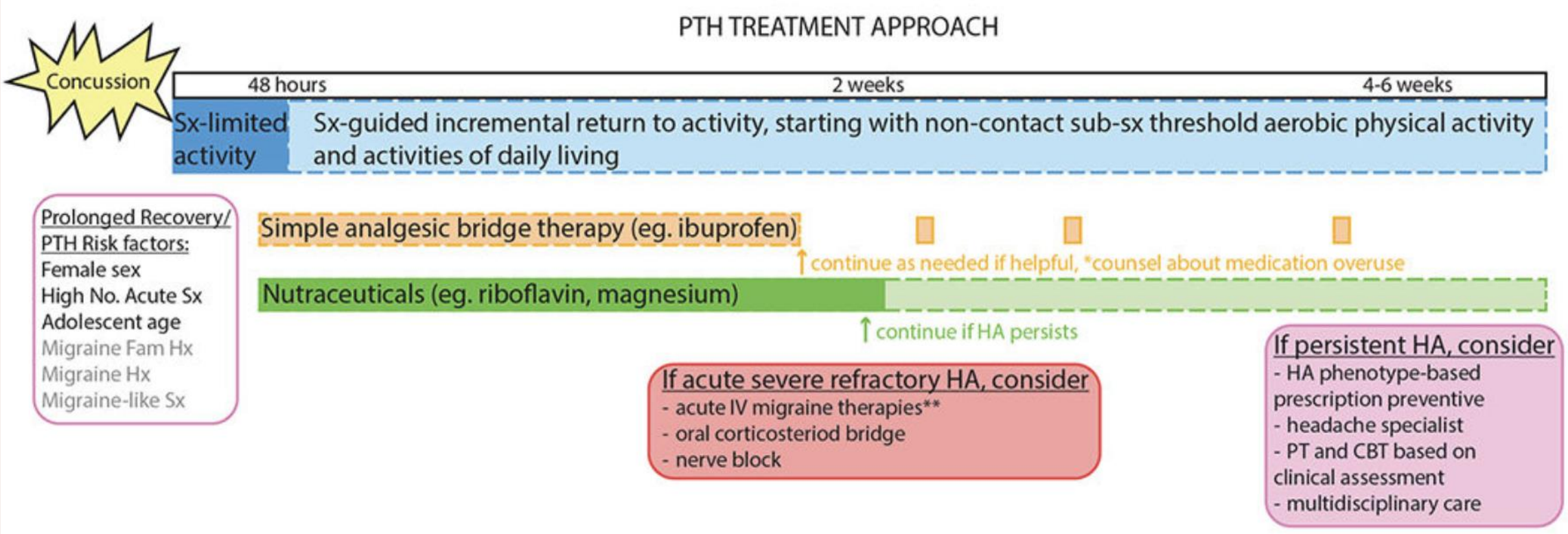

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Activity intolerance

Traditional management was "cocooning" with strict cognitive + physical rest until symptom resolution

Recent evidence that symptomatic exacerbations may be correlated with HR

Treatment!

Current pediatric mTBI recommendations:

- Strict activity restriction x24-48 hours
- Gradual return to play and activities. Avoid continued restriction.
- Subthreshold activity in all domains.

1. Leddy JJ. Sport-Related Concussion. N Engl J Med. 2025 Jan 30;392(5):483-493. doi: 10.1056/NEJMcp2400691. PMID: 39879594.

Neurology et al resources

Migraine Buddy – app for migraine calendar tracking

PocketEyeExam – has Ishihara, OKN, visual acuity (can use Eye Handbook for more testing options, but more clunky)

OpenEvidence – a nice first line GPT like resource for open-source article summarization and distillation. Can do PA letters as well.

EpilepsyPredictionTools.Info – MDCalc of seizure calculations. Lots of caveats, but based on some evidence

Epic released SCAT5 questionnaire. CATTonline.com/scat for digital version.

Infantile Spasms Action Network

For functional neurological disorder / symptoms:

- FNDhope.org
- Neurosymptoms.com

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Thank you!

Feel free to contact me on Epic, email (Austin.Layton@providence.org) or phone (503-907-4060)

p.s. our wait time for new patients is ~2 weeks right now 😇