Neurologic Manifestations of Systemic Lupus

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Conflicts of Interest

- I have many relationships with pharmaceutical firms and nonprofits organizations.
- These relationships largely support either my clinical trial activities or patient support efforts.
  - Some of my conflicts do support physician or patient education activities for commercially available therapies. The companies that support those talks are hoping they will result in increased sales.
- These relationships are reported to Michigan State University and to the Federal Government.
- I do not believe any of these relationships will conflict with the topics of the talk today.
- My talk today is not being sponsored by any pharmaceutical firm

Who is this Sachdev guy?

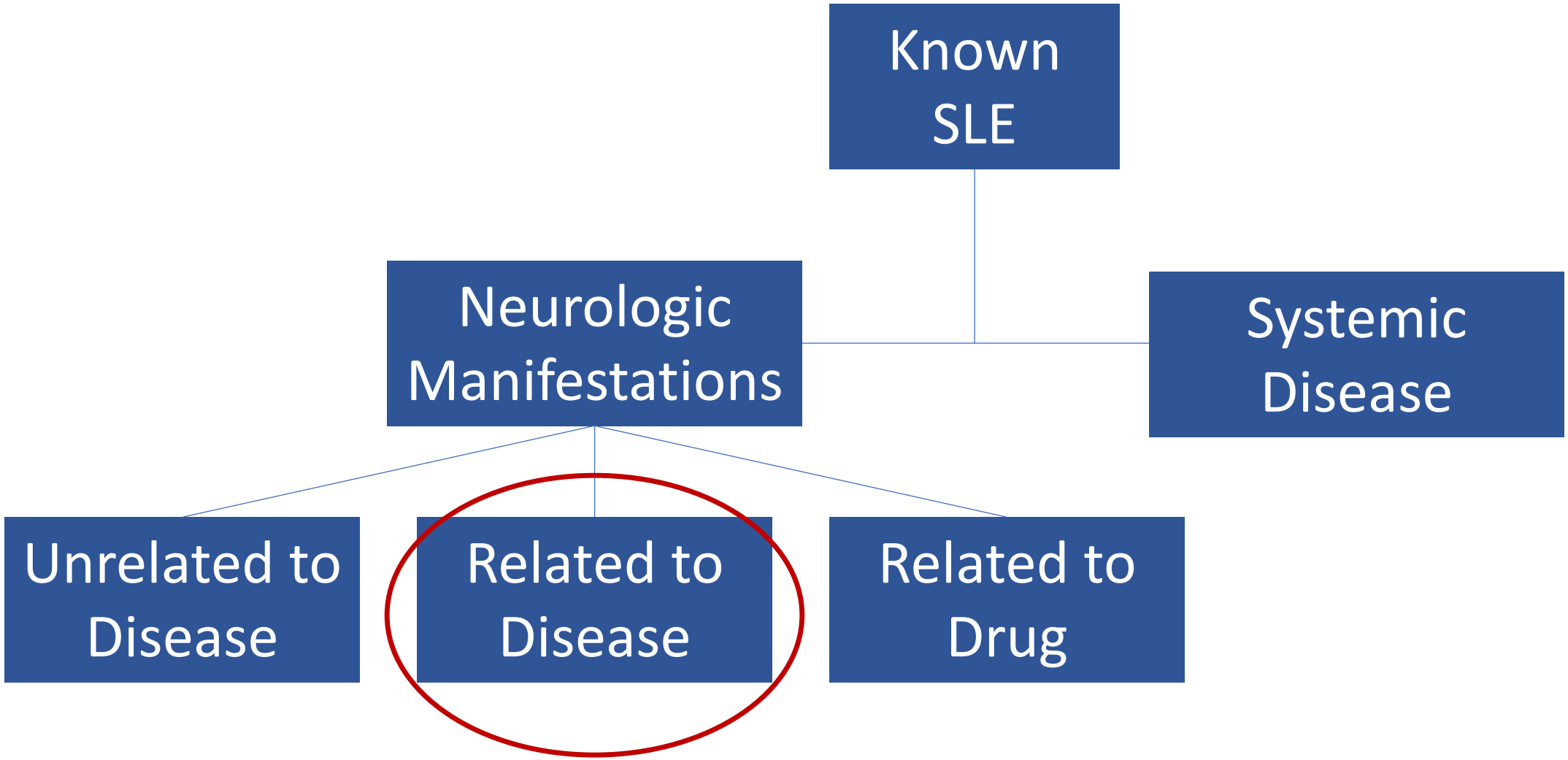
- Associate Chief Medical Officer – I care a lot about delivery of care
- Active clinical trialist – I am the principal investigator on ~$1,300,000 in clinical trial activity, primarily in degenerative brain disease/dementia as well as autoimmune disorders
- Active clinician – I see several thousand patients per year in the hospital and in the clinic
- Rare disease expert – I am the principal investigator and responsibility party for our Muscle Dystrophy Association grant and clinic
- A Michigander – having lived here all my life, found a wife who is also a Michigander and produced three children who we are raising in this community

Road Map

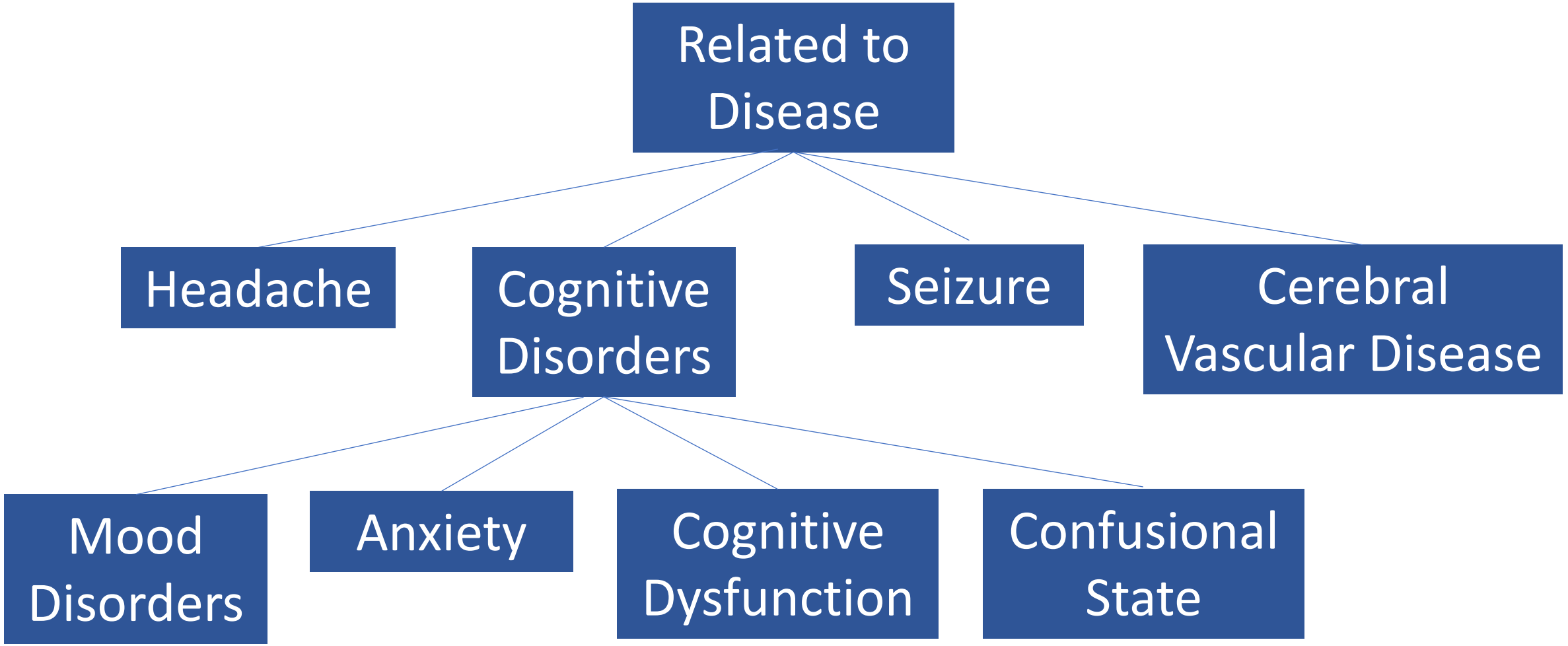
- Start big – the spectrum of neurologic complaints in SLE patients
  - This section is going to feel clumsy
- Meet Martha Washington, she has headaches
- Meet more famous people while we talk about:
  - Mental health
  - Body pain
- Wrap up

Section 1 – All the neurologic things

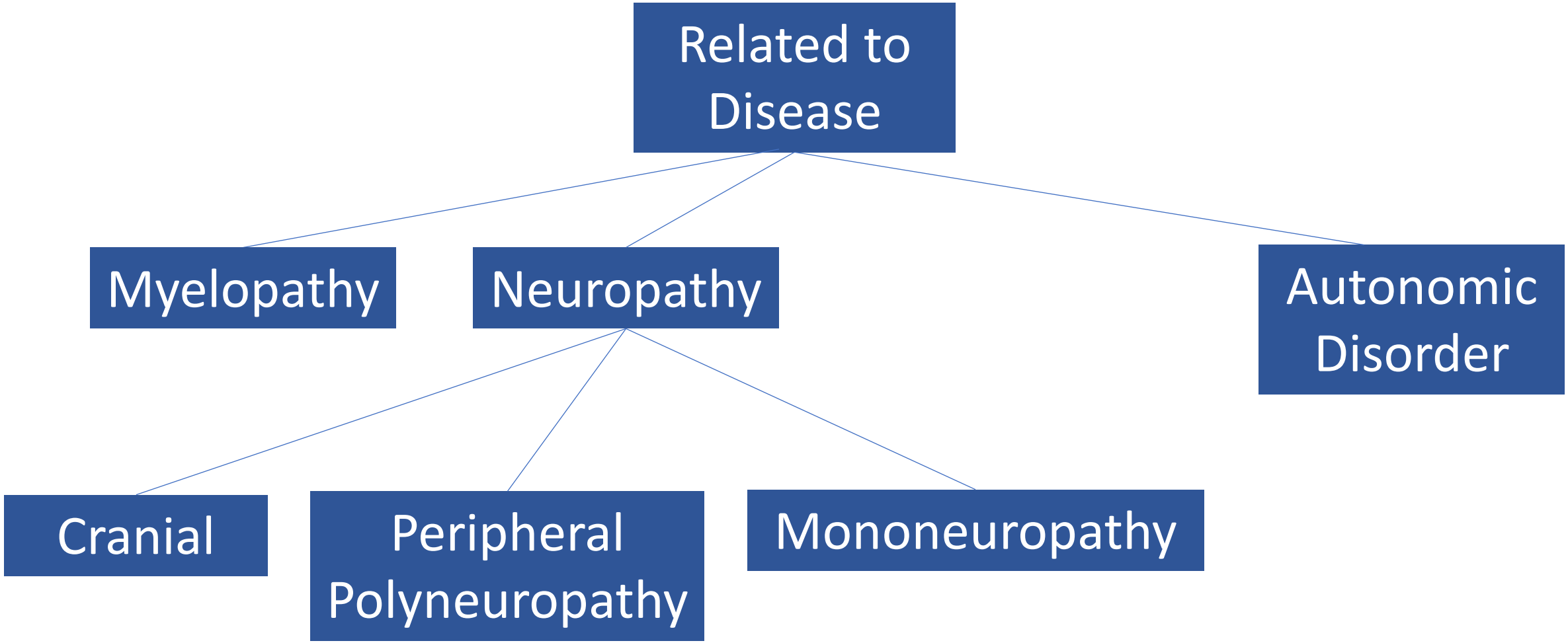
Approach to this talk



Styles of Cerebral Neurologic Symptoms



Styles of Peripheral Neurologic Symptoms



51% of patients with known SLE will have some neurologic issue within 15 months of diagnosis

- 90% or more of those with neurologic issues will have CNS disease
- 80% will have generalized symptoms, rather than focal

All of this sounds bad

•. **Prospective analysis of neuropsychiatric events in an AA disease inception cohort of patients with systemic lupus eryth**
J G Hanly[1], 2010 Mar;69(3):529-35.

Most SLE Patients will never have a sinister neurologic manifestation of the disease

- Johns Hopkins SLE clinic choses to highlight:
  - Cognitive Dysfunction
  - Headache
  - Fibromyalgia
  - Organic Brain Syndrome
  - CNS Vasculitis

https://www.hopkinslupus.org/lupus-info/lupus-affects-body/lupus-nervous-system/#:~:text=About%2020%25%20of%20patients%20with,usually%20requires%20corticosteroids%20for%20treatment.

Bottom line – Section 1 – All the neurologic things

- Neurologic signs and symptoms are common in SLE patients – 50% in 18 months post diagnosis
- The vast majority of SLE patients will not have a life or organ threatening neurologic complication from their SLE
- The potential types of complications are typically “inside the skull” like headaches and mental fog rather than “outside the skull” like numbness and falls

So…what does this all look like?

- Let’s go complaint by complaint

Section 2 – This talk is making my head hurt

Let’s meet Martha

Martha is 26. She is a retail employee doing stock and customer service. She was diagnosed with SLE at the age of 24 with unexplained joint pains and a malar rash. With treatment, her joint pains and rash have improved but she has some aching body pain and has developed moderate intensity pounding headaches 6 times per month. The pain is in her temples. She is sensitive to light and sound and calls off work once a month due to this issue.

Martha Washington – the 1st First Lady

SLE and Headache

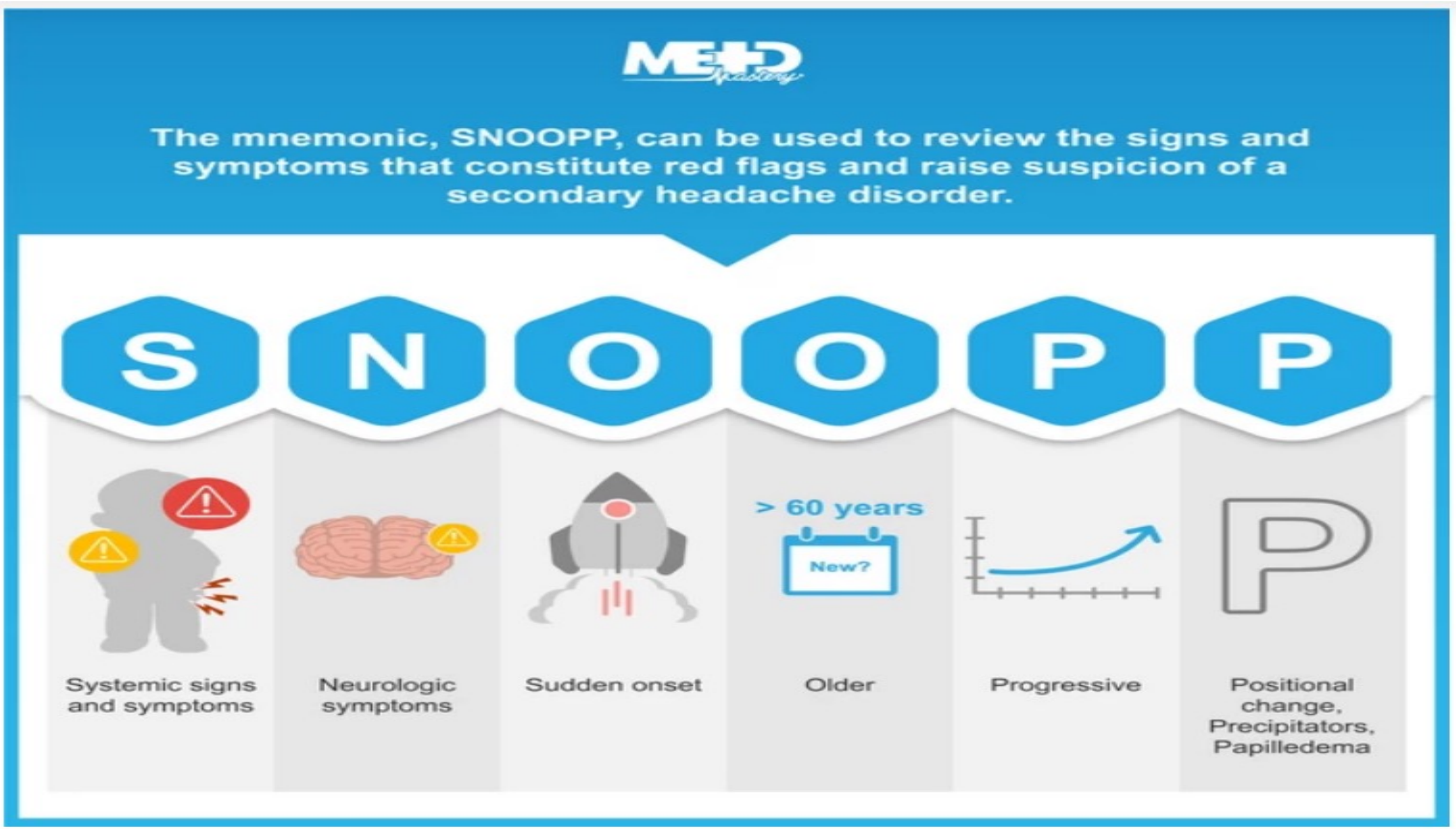
- 17.8% of patients have headache
  - Migraine [60.7%],
  - Tension [38.6%],
  - Intractable nonspecific [7.1%]
  - Cluster [2.6%]
  - Intracranial hypertension [1.0%]
- Very similar to the general population

Headache in systemic lupus erythematosus: results from a prospective, international inception cohort study

John G Hanly 2013 Nov;65(11):2887-97.

In general, treat your headaches like headaches

- Headache does not correlate with disease severity
- In general does not indicate that your treatments are failing
- HANLY ET AL:
  - Conclusion**:** Headache is frequent in SLE, but overall, it is not associated with global disease activity or specific autoantibodies. Although headaches are associated with a lower HRQOL, the majority of headaches resolve over time, independent of lupus-specific therapies.



https://www.medmastery.com/guides/headaches-clinical-guide/recognizing-red-flags-headache-history-snoopp

“Lupus Headache”

- Uncommon disease process
  - Lupus meningitis
  - Lupus vasculitis
- These are not benign; they are often life or brain threatening
- Escalate very quickly
- The headache is one element of a major symptom complex
- MRI BRAIN, CT Angiogram head and spinal tap are required

IDCases. 2020; 21: Meningitis as the initial manifestation of systemic lupus erythematosus. Nada Al Mahmeed,[a]

Returning to Martha

- Migraine is diagnosed based on the style and location of headache.
- The pattern of headache is most important
- What is someone like Martha to do?
  - Talk to your provider
  - Try supplements first, the American Migraine Foundation discusses:
    - Magnesium
    - Riboflavin

Bottom Line – Section 2 - Headaches

- Most headaches are just headaches
- That doesn't mean you shouldn't try to break the headache, but it does mean that, typically, you would not change your lupus medicines because of the headaches
- Trying a supplement for 8-12 weeks with regular daily dosing is one strategy
- RED FLAGS prompt more evaluation – MRI BRAIN, CT Angiogram and Lumbar Puncture
- SLE can attack the brain causing headaches, but this is fairly uncommon

Section 3 – I am not quite thinking straight

Rare Bored Ape Yacht Club NFT Sells for Record $3.4 Million USD

According to Sotheby's, less than 1% of Bored Ape NFTs have gold fur.

https://hypebeast.com/2021/10/bored-ape-yacht-club-nft-3-4-million-record-sothebys-metaverse

Section 3 - Lupus and Cognitive Disorders

ChatGPT

Lupus, being a chronic autoimmune disease, can significantly impact a person's emotional well-being, and depression is a common mental health issue associated with lupus. Here are some reasons why lupus may contribute to depression:

1.

Chronic Illness Stress: Coping with a chronic illness like lupus can be overwhelming. The uncertainty of symptoms, the need for ongoing medical care, and the impact on daily life can lead to chronic stress, which is a risk factor for depression.

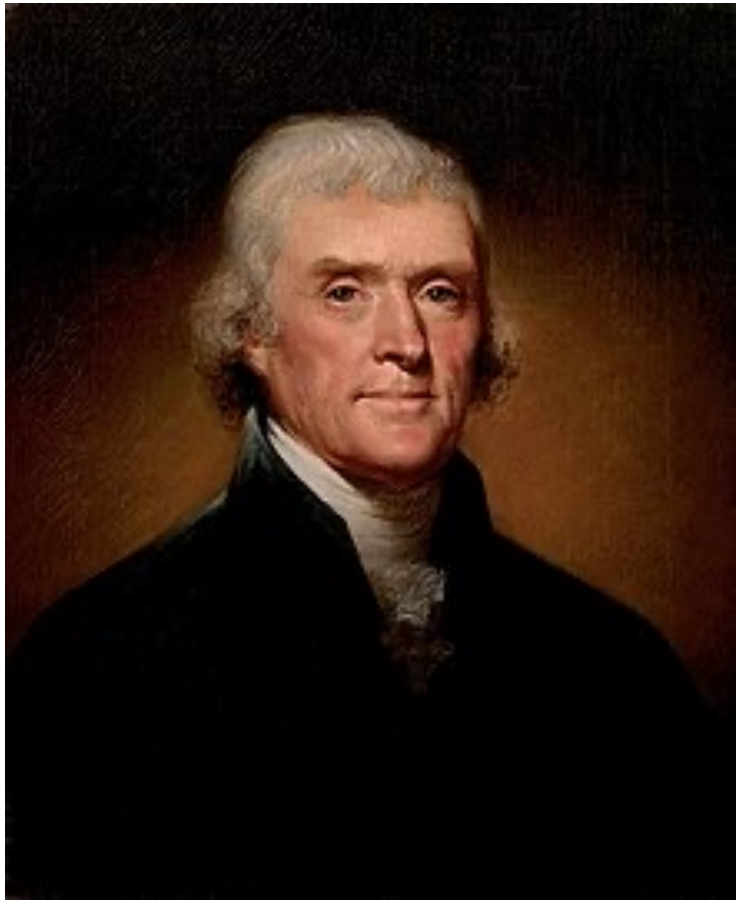
AI is not actually intelligent, its just good at aggregating public information

- The most common position statement is that, if you have Lupus and you have cognitive issues that YOU are not COPING with your reality.
- This is unfair

Public Opinion

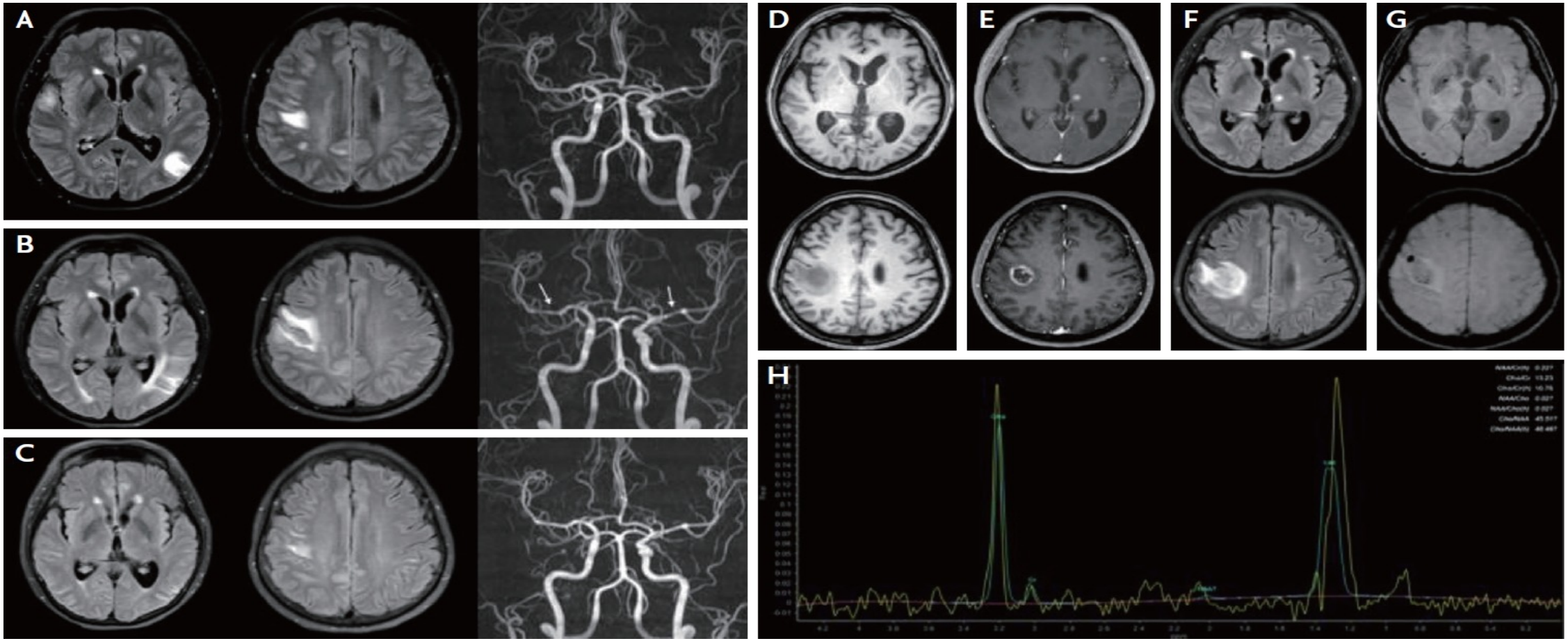
Meet Thomas

31-year-old, employed in sales, has four years of progressive malar rash and joint pain. He did not seek care. Acutely, his wife notices changes to his speech. His job performance suffers. He begins to talk about government surveillance and starts driving the family garbage to a dumpster rather than having the city pick it up at the curb. His wife becomes concerned and brings him to an urgent care. He is sent into the emergency department and admitted.



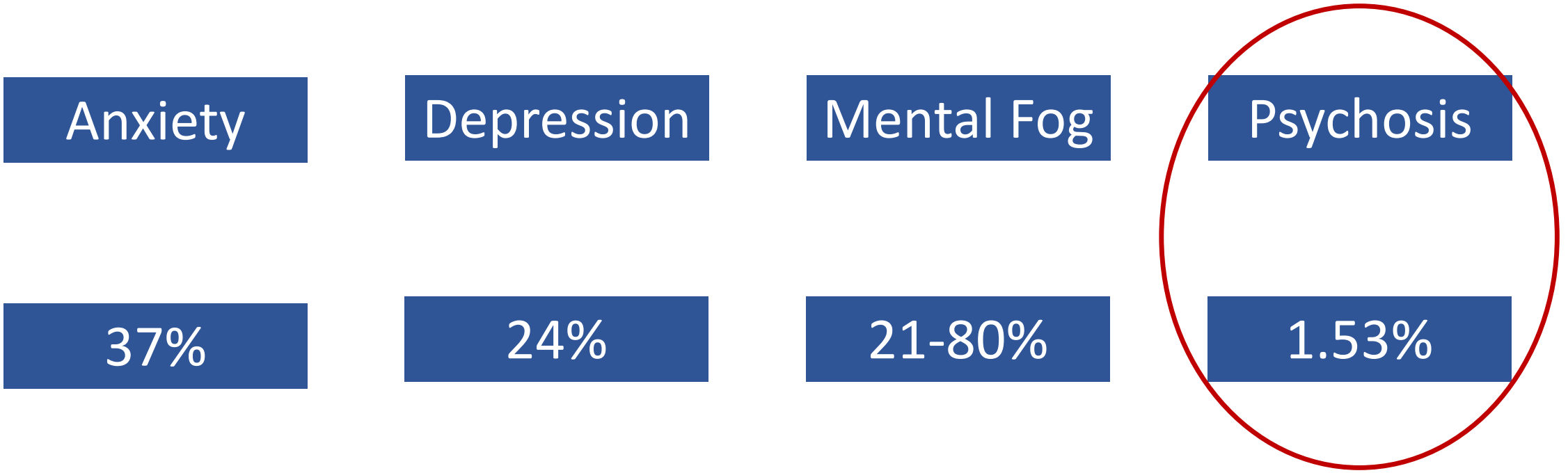
Thomas Jefferson – Third President

Cognitive changes can be a worrisome sign in SLE Patients



J Neurosonol Neuroimag 2022; 14(2): 82-85. Recurrent Neuropsychiatric Systemic Lupus Erythematosus Presenting with Primary Central Nervous System Lymphoma. Jun Kyu Song, MD*

Most SLE patients with cognitive changes do not have organ threatening disease



John G. Hanly MD, **Volume71, Issue2. F**ebruary 2019. Pages 281-289

Zhang. BMC Psychiatry **volume 17**, Article number: 70 (2017)

Psychosis

- Can be hard to identify:

Paranoia

Social Withdrawal

Auditory Hallucination

Lack of Empathy

Disruption Visual-Spatial

Confused Speech

Visual Hallucinations

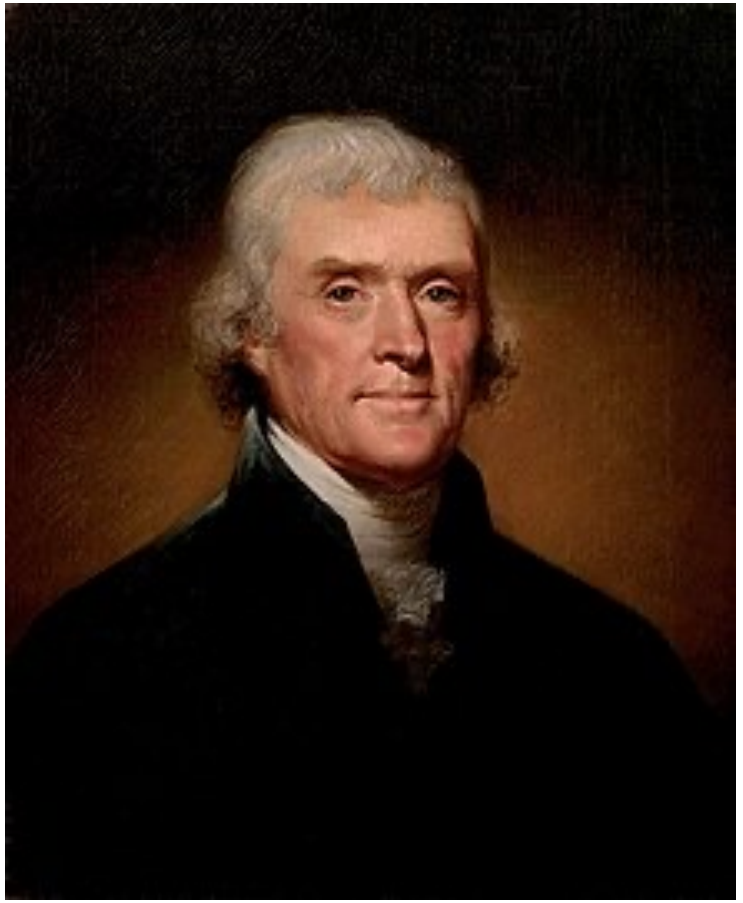
https://www.nimh.nih.gov/health/publications/understanding-psychosis

Psychosis and SLE

- Must consider lupus cerebritis
- Must consider lupus associated aseptic meningitis
- Most patients improve with standard therapies against the systemic disease process
- Hospitalization is often indicated if this symptom complex is present and **direct brain injury or irritation is suspected**

Continuing with Thomas

Lupus cerebritis was diagnosed at the hospital and he was treated. His joint pain is better, his rash is clearing, and he is no longer concerned about government surveillance. He returns to work but isn't as sharp as he used to be or as organized. He takes his medicine. He feels like he is always "one step behind" where he should be.



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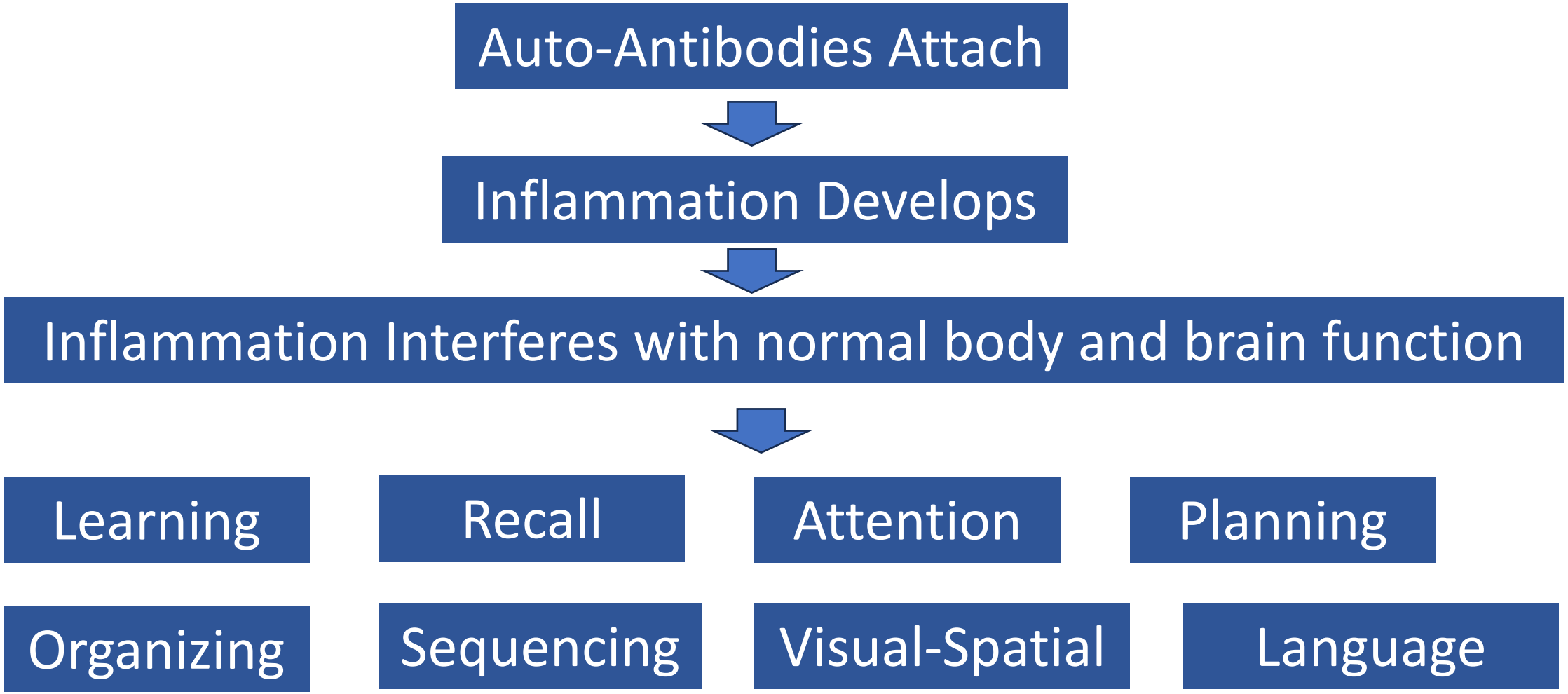
Direct vs. Indirect Brain Injury

- Direct – the brain and its structures are under attack
- Indirect – the brain is irritated but not injured

Brain Fog maybe reflect inflammation



. Seet et al. 2021 Jun;8(2):651-679. doi: 10.1007/s40744-021-00312-0.

Brain Fog may require a change in treatment

- Blood markers, including cytokine levels, complement levels and acute phase reactants are all available
- Yet, burden of illness is best measured clinically
- For some patients, a burst of prednisone may be a useful trial

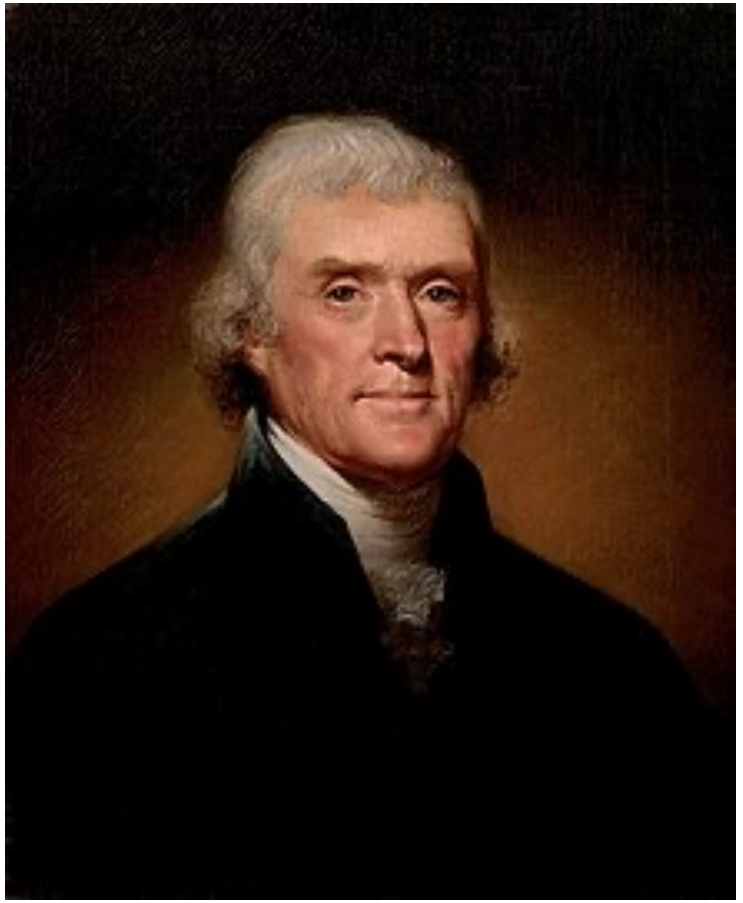
J Clin Med. 2023 Jun; 12(11): 3639.

What if I am uncomfortable with more immune suppression?

- Off label use of stimulant medications can be tried:
  - Modafinil (Provigil)
  - Armodafinil (Nuvigil)
  - Amphetamine (Adderall)
- Diet and exercise make a difference
- Accepting a “new you” might be part of the conversation. There are many “brain types” and transitions in life are, to some extent, a part of living

Wrapping up with Thomas

With his second and third visits, his medications are adjusted. His brain fog persists but gets better to some extent. He really needs to return back to a very high level of function because of his work in sales. The topic of medication to improve attention is raised. Some lingering depression is identified, and he is also referred to a therapist.



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Bottom Line – Section 3 - Cognition

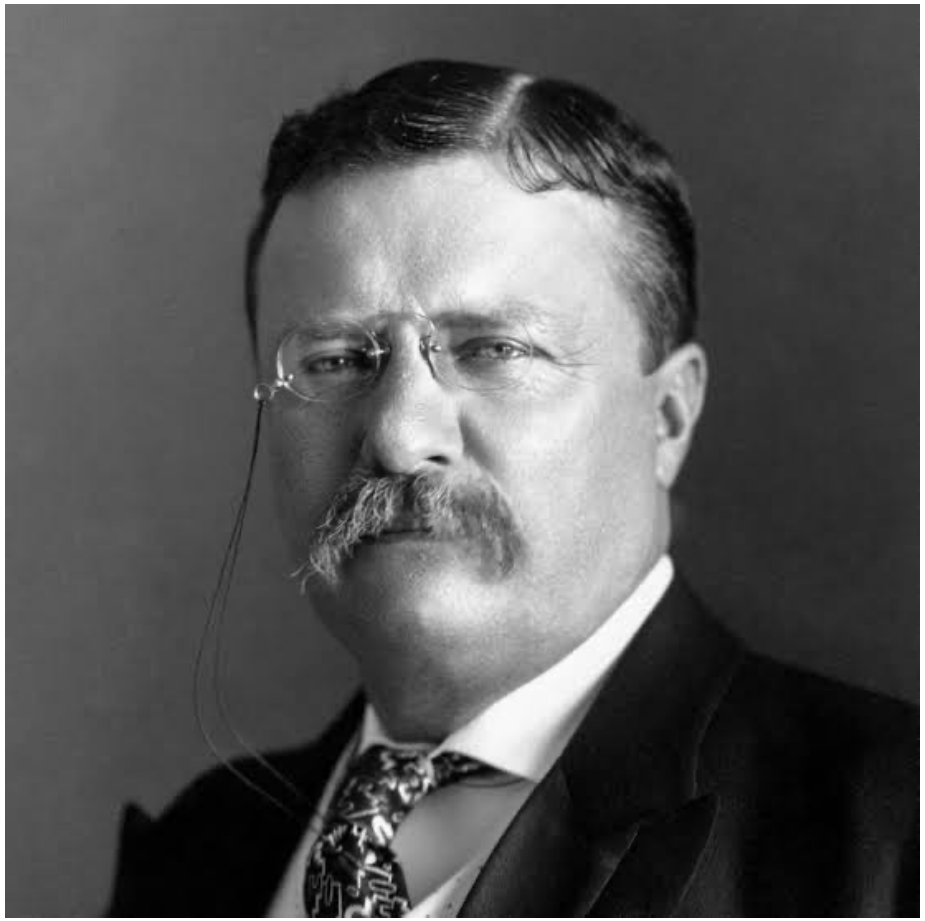
- Cognitive changes encompass a broad array of types of symptoms
  - Anxiety and depression can be seen and are treated with medications and therapists
  - Psychosis is concerning and should prompt a robust medical evaluation
  - Brain fog is also concerning and should prompt a discussion about medications for inflammation.
    - Some patients can benefit from medications to improve wakefulness, but these are controlled substances and off-label

Section 4 - Fibromyalgia

- This section is going to hurt

Meet Teddy

Teddy is a 21-year-old college student who has developed widespread body pain but no other significant symptoms. He does have “rosy cheeks” but he is native to Florida and came to Michigan State on an e-sports scholarship. He just assumed his cheeks were not made for the cold. His body pain makes it difficult to stay in his seat for too long. He is concerned about his spot on the team.



Theodore Roosevelt, 26th president

Symptoms of Fibromyalgia

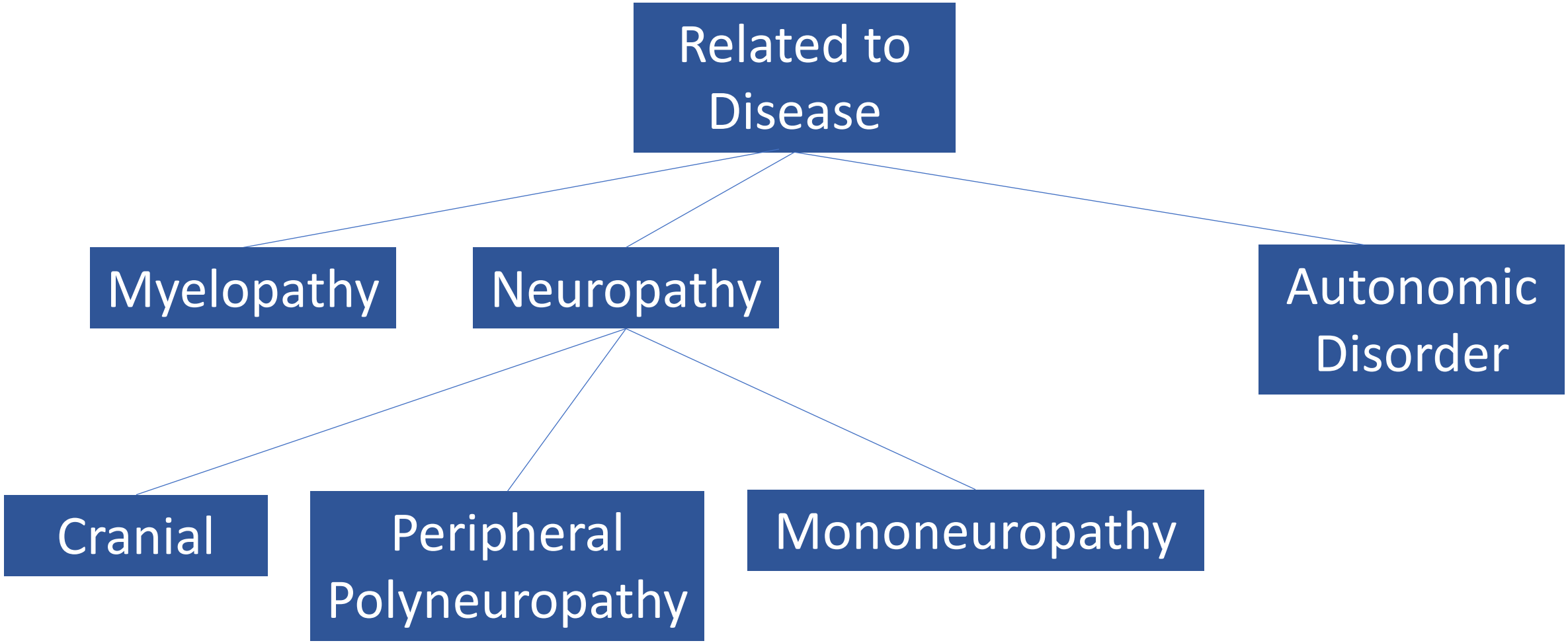
The main symptoms of fibromyalgia are:

- Chronic, widespread pain throughout the body or at multiple sites. Pain is often felt in the arms, legs, head, chest, abdomen, back, and buttocks. People often describe it as aching, burning, or throbbing.
- Fatigue or an overwhelming feeling of being tired.
- Trouble sleeping.

The MSU Neuromuscular Approach

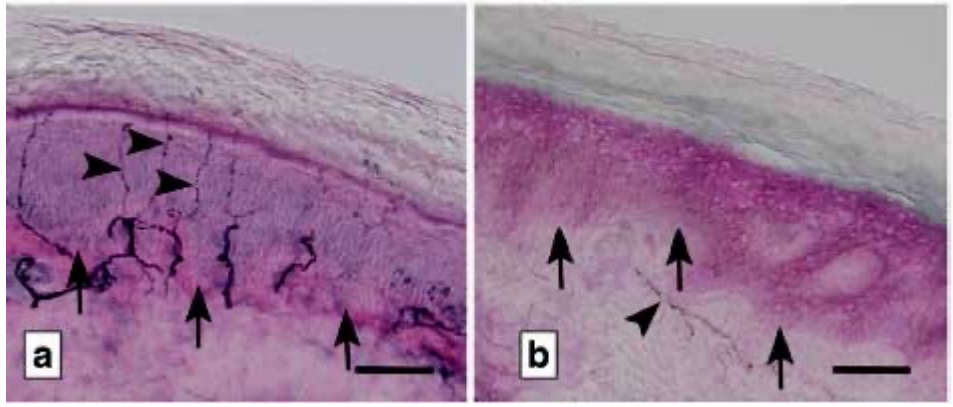
- The cause of fibromyalgia is not known.
- Fibromyalgia is not thought to reflect a brain or tissue injury, so symptom management is the next step
- We will look to make sure that the body and neuropathic pains felt by the patient are not actually coming from damage to the neurologic structures from the neck down.

Styles of Peripheral Neurologic Symptoms



Skin Biopsy and EMG

- 3 site skin biopsy establishes the health of small nerve endings



https://www.healthrising.org/blog/2016/02/07/diagnosing-fibromyalgia-small-nerve-fiber/

- EMG establishes the health of large nerve endings

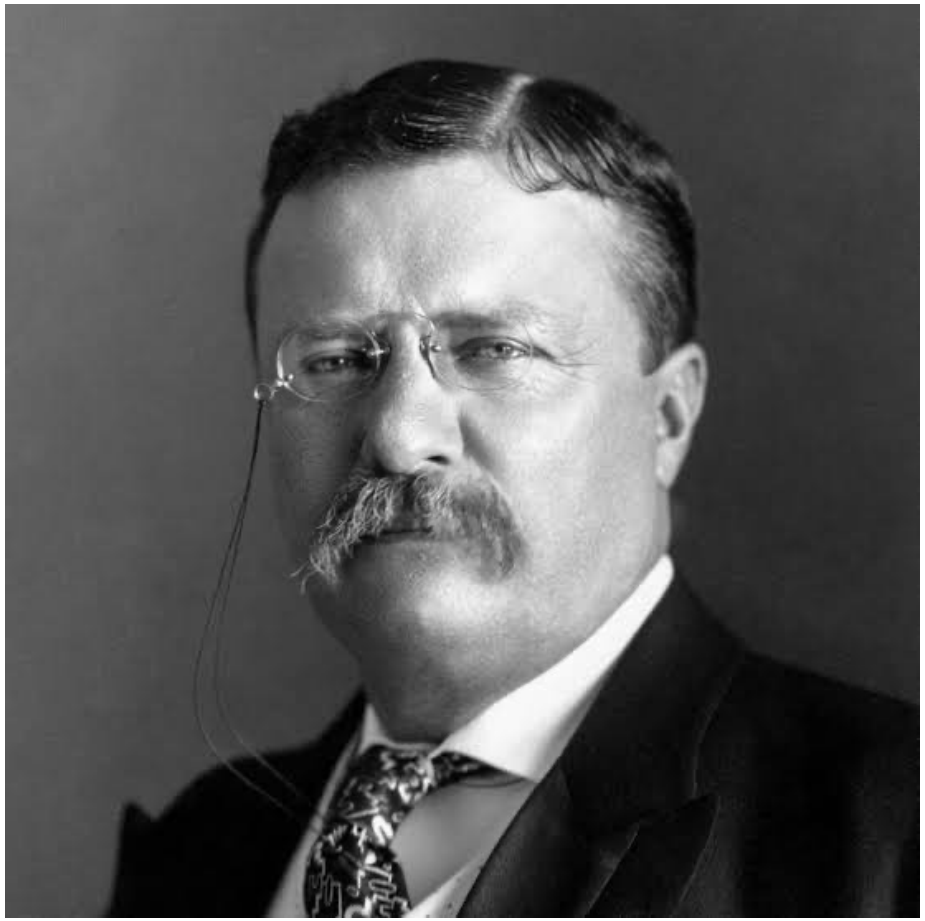
https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/electromyography-emg

What do to with the results?

- If a neuropathy is identified, then that leads to the question
  - Why are these nerves damaged?
  - Could it be the SLE?
- If the nerves are not damaged, then we ask if another site could be injured. For example, muscle.
- If no other site is found, then this is fibromyalgia. In that case, symptom management is pursued.

Teddy Continued

Teddy undergoes skin biopsy and EMG. No nerve injury is found. He is diagnosed with blood markers for SLE. Treatment is tried and his level of energy feels better but he still has pain. Fibromyalgia is diagnosed and treatments are offered.



Theodore Roosevelt, 26th president

What are the medication options?

- For fibromyalgia – FDA approved therapies
  - Duloxetine (Cymbalta) – selective serotonin and norepinephrine reuptake inhibitor
  - Milnacipran (Savella) – selective serotonin and norepinephrine reuptake inhibitor
  - Pregabalin – reduces calcium channel activity

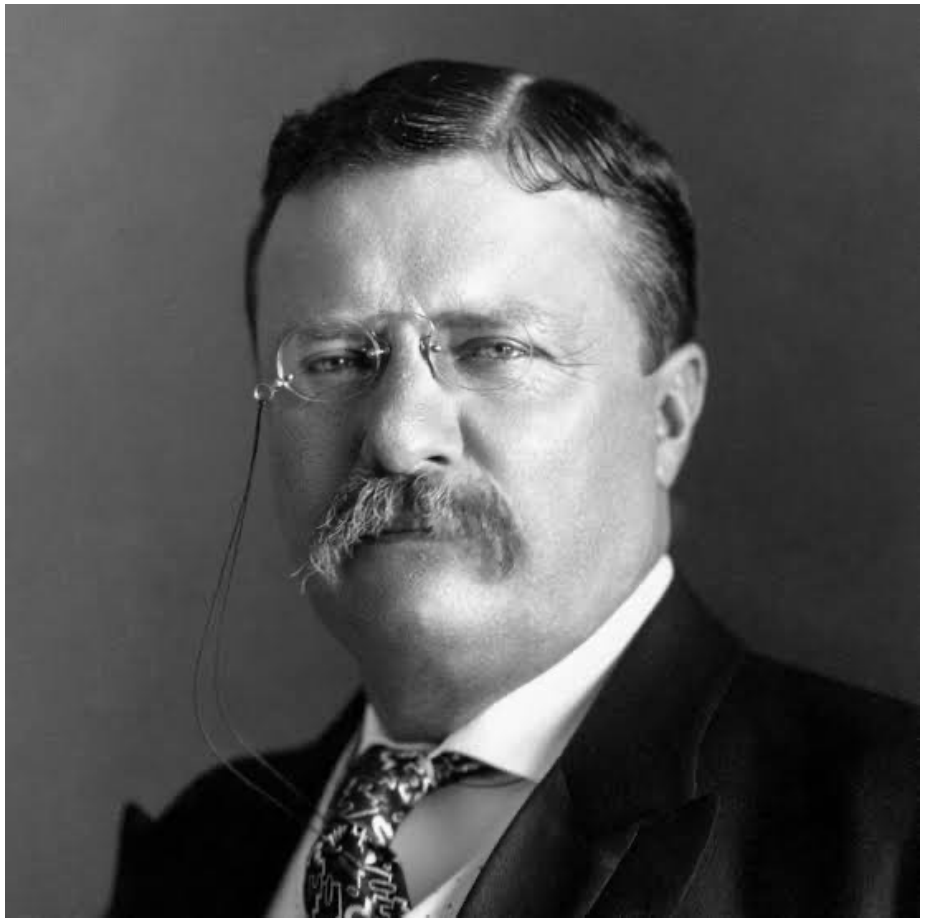
- Neuropathic pain – Not FDA approved for Fibromyalgia
  - Amitriptyline/ Nortriptyline – Tricyclic antidepressant
  - Gabapentin - reduces calcium channel activity

What are medication options?

- Muscle relaxants – off label use
  - Cyclobenzaprine - Alpha 2 – Adrenoceptor agonist
  - Baclofen – GABA-B agonist

Teddy Summary

Teddy elects to take the mixture of duloxetine and pregabalin. They are both brain drugs, so he has some daytime sleepiness and some mental fog. He laments that he cannot drink alcohol on these drugs. His pain is better controlled, and his mood is better. His ability to play Grand Theft Auto at a competitive level is preserved. While she is happy that he is no longer in pain and supportive of her son, his mother continues to wonder about “e-sports.”



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Bottom Line – Section 4 - Fibromyalgia

- Body pain co-exists with SLE in many patients.
- An evaluation of the causes of body pain is reasonable, because SLE can be associated with injury to nerves and muscles.
- If nerve injury is identified, then a change in immune management may be reasonable.
- If no nerve injury is identified, then symptom management may be the right answer.
- FDA approved symptom management options exist

Wrap up

- Many patients with SLE have neurologic symptoms
- While many rare disorders can exist, the most common types of presentations are:
  - Headache
  - Cognitive Disorders
  - Body pains
- These presentations can lead to changes in immune therapies and so these complaints should be pursued.

Thank you!

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