

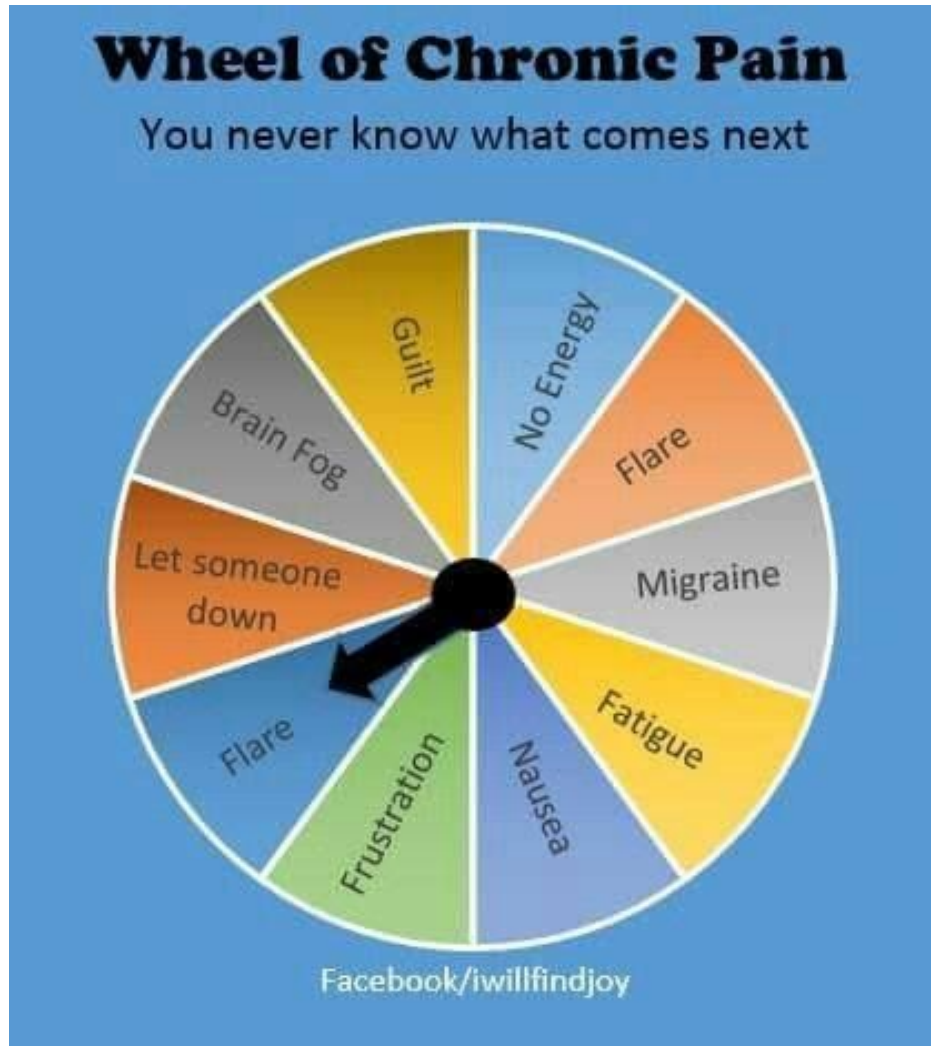


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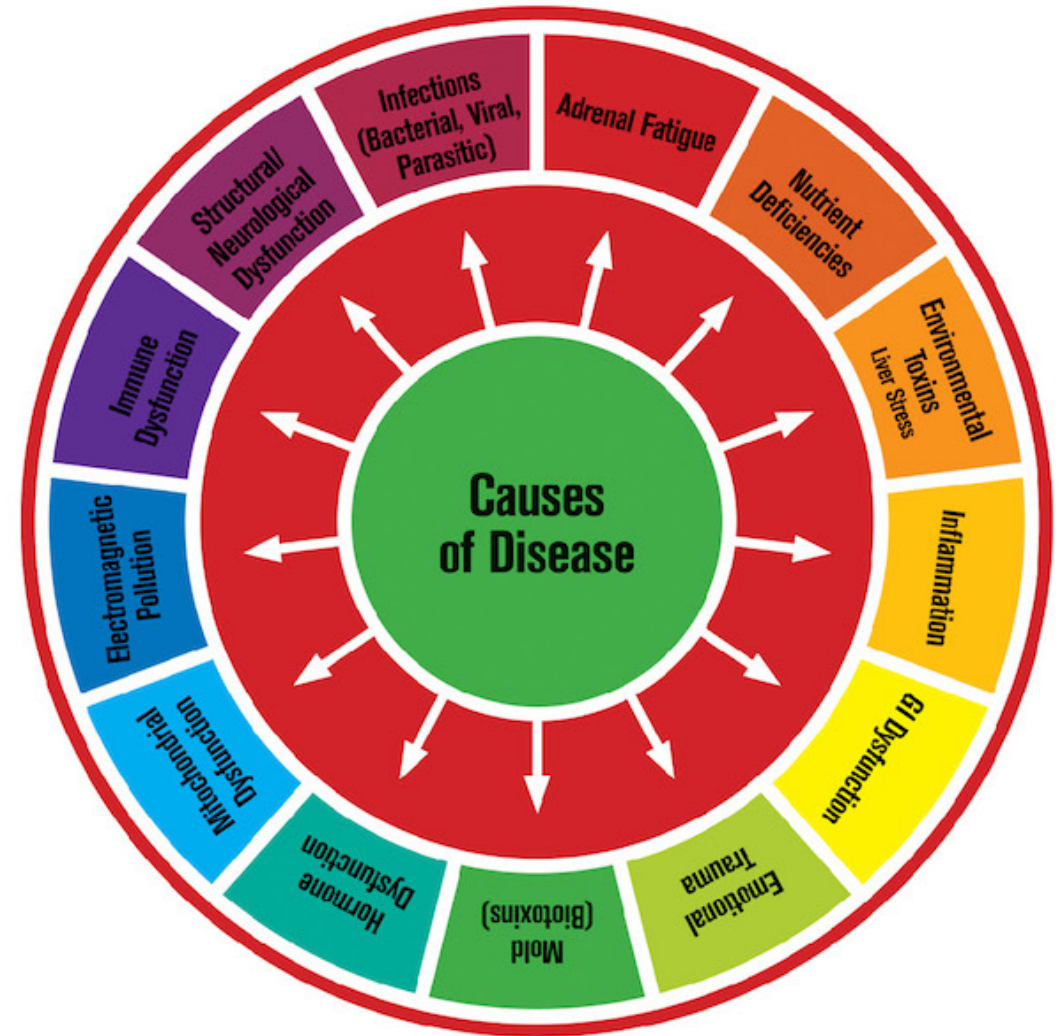
# UNRAVELING THE COMPLEXITIES OF CHRONIC PAIN AND FATIGUE – PART 2

*BRAYDEN YELLMAN, MD & LUCINDA BATEMAN, MD*

# NOTABLE COMORBIDITIES IN THOSE WITH CHRONIC PAIN AND FATIGUE



Patient's Thoughts

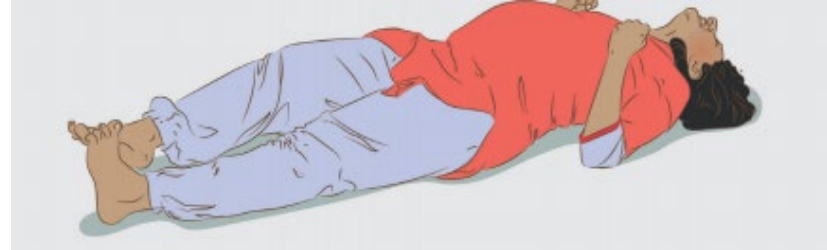


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Practitioner's Thoughts

# OUR PATIENT: 31 Y.O. FEMALE

Chief Complaint: seizures and increasing diffuse muscular pain



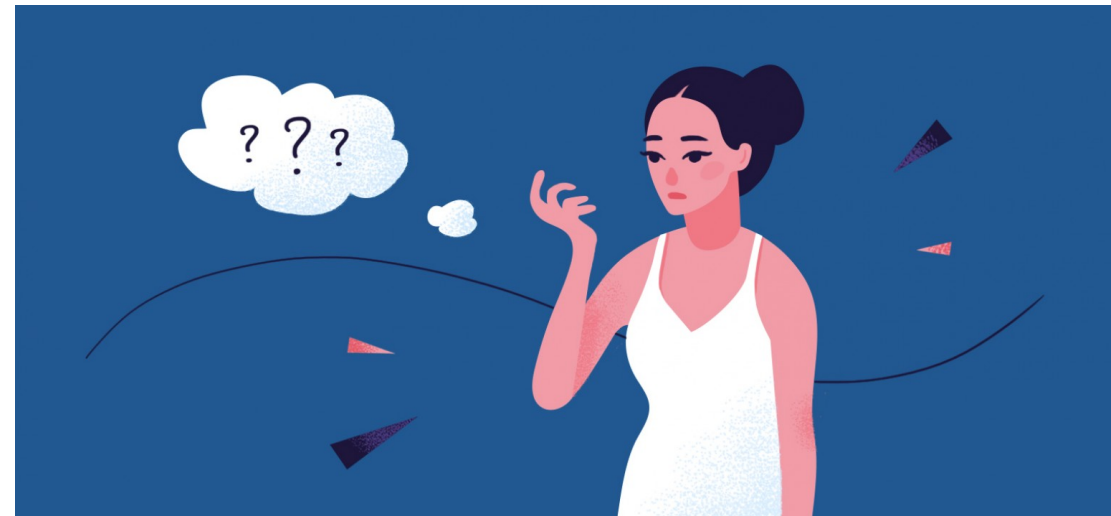
## HPI:

- Had been noting nausea and anorexia earlier in the day, took a nap
- After the nap, got up to take a shower
- Nausea, rapid heart rate, facial flushing, anxiety all increased while showering and she ended her shower early after 1-2 minutes
- Stepped out of the shower, standing in front of the mirror, started to dry her hair
- Began to experience moderate amplitude “tremors” in both upper extremities and within the neck
- Became disoriented, somewhat unresponsive to nearby husband
- Then experienced an episode of syncope, may have “bumped” the side of her head on the edge of the bathroom counter during syncope

# OUR PATIENT: 31 Y.O. FEMALE

## HPI (continued):

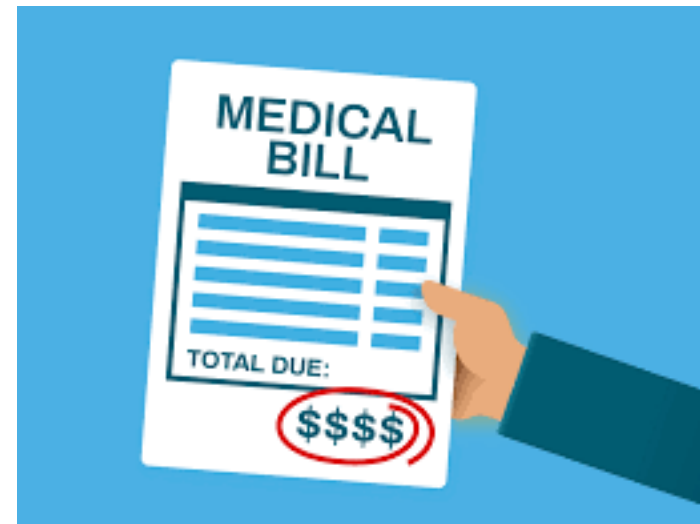
- No true loss of consciousness
- Duration of tremors prior to syncope was about 30 seconds
- Husband reports 30 minutes of post-ictal confusion, word-finding difficulties, disorientation
- No preceding aura
- No loss of bowel or bladder continence
- No tongue biting
- No new medications or supplements
- Denies EtOH, tobacco, illicit drug use



# OUR PATIENT: 31 Y.O. FEMALE

## HPI (continued):

- Over past two years, had experienced perhaps ten similar but “milder tremoring episodes” without syncope, though she would usually lie down upon symptom onset
- Recent non-febrile upper respiratory illness w rhinorrhea, sinus pain, anterior cervical LAD, cough in setting of known sick contact: daughter
- Stressful home situation due to increasing medical bills for patient’s recurrent trips to various medical specialists
- Patient’s grandmother recently passed away



# OUR PATIENT: 31 Y.O. FEMALE

## PMH:

- Depression
- Chronic Pain
- Generalized Anxiety Disorder
- Chronic Migraines
- Panic Attacks
- ADHD
- Eczema
- Raynaud's
- IBS
- Exercise-Induced Asthma
- Seasonal Allergic Rhinitis
- Dysmenorrhea
- Interstitial Cystitis

## SH:

- No tobacco, drugs
- Rare EtOH, feels "sick" after drinking
- Gymnastics when young, but no sports after grade school
- Associates Degree
- Worked at the front desk in a chiropractic office for a few years
- Homemaker
- 2 children, 1 dog



## PSH:

- Cholecystectomy
- Left foot Lisfranc fracture s/p ORIF

## FH:

- Father – Prostate CA
- Mother – Chronic Fatigue Syndrome
- Sister – Anxiety D/O



# OUR PATIENT: 31 Y.O. FEMALE

## Medications:

- Albuterol (prn)
- Bupropion
- Rizatriptan
- Lorazepam (prn panic attack)
- Hyoscyamine
- Kyleena OCP
- Thiamine
- Zinc
- Vitamin D
- Vitamin B12
- Vitamin C
- Ferrous Sulfate
- Arginine
- Glucosamine
- Probiotics
- Co-Q-10
- Melatonin



## Allergies:

- Fluoxetine
- Escitalopram
- Buspirone
- Topiramate
- Alprazolam
- Ciprofloxacin
- Fluticasone (nasal)
- Perfume
- Lemons
- Baking Soda
- Febreze
- Jell-O
- Paint
- Play-Doh
- Watermelon
- Mites
- Molds
- Band-Aid Adhesive
- Bananas
- Latex



# OUR PATIENT: 31 Y.O. FEMALE

## Cardiology:

- Vitals: T: 98.6, HR: 107, BP: 102/68, RR: 14, SpO2: 97%
- Normal heart and lung physical exam
- CMP, CBC, ESR, CRP, ANA, CPK, troponin, TSH, lactate all normal
- Sinus tachycardia on 48-hour Holter monitor
- Normal transthoracic echocardiogram
- Syncope episode not thought to be cardiogenic



## Neurologist:

- Tremors not consistent with tonic-clonic movements
- Normal neurological exam in clinic
- MRI of brain unremarkable for masses, demyelinating disease, MTS
- EEG study without epileptiform activity
- No indication for epilepsy video monitoring unit study
- No limitations on driving
- No AED's prescribed
- Asked to consider seeking care from behavioral health



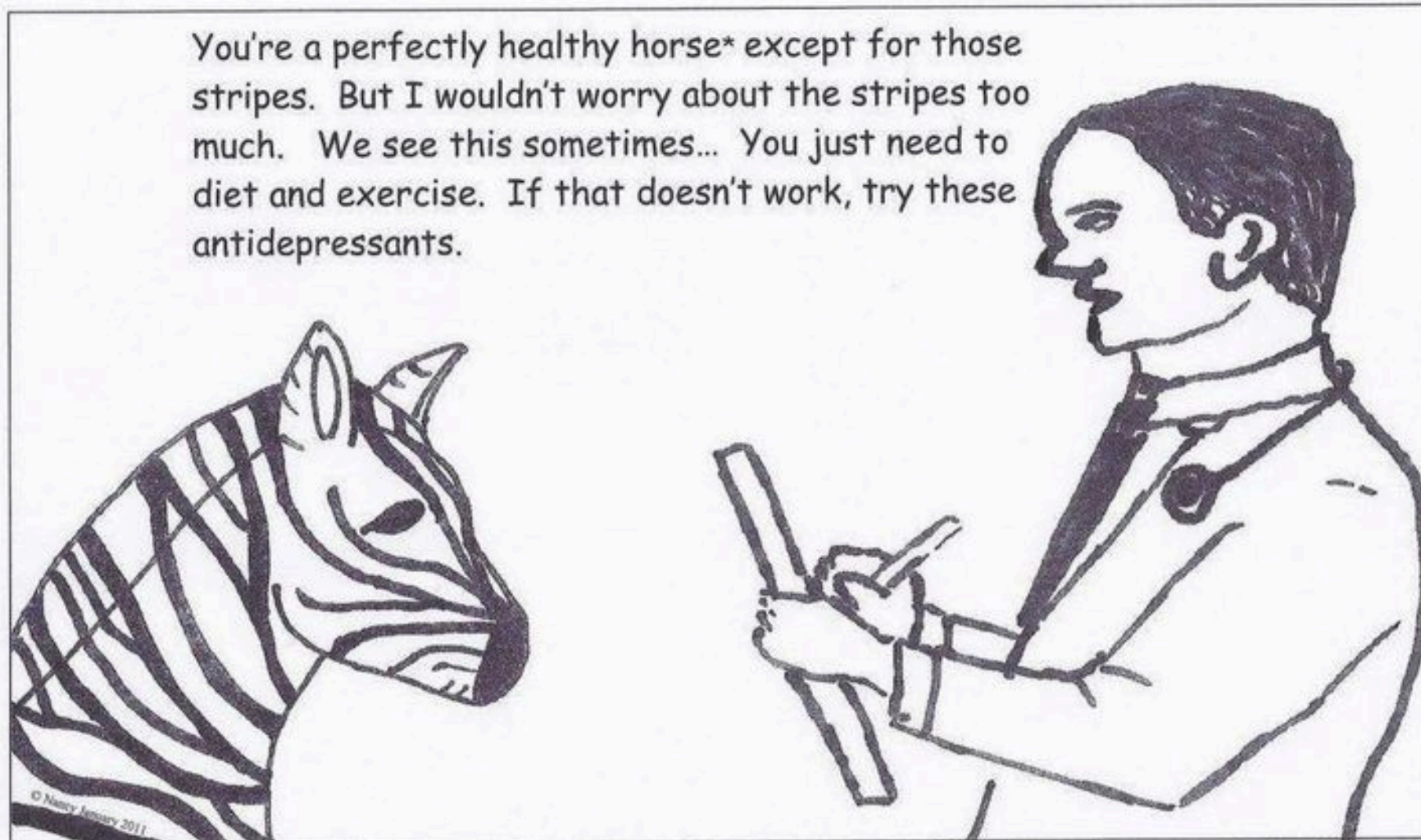


OUR PATIENT: SHE NOW PRESENTS  
TO YOUR OFFICE FOR HELP...



# Pseudoseizure?

# OUR PATIENT: SHE NOW PRESENTS TO YOUR OFFICE FOR HELP...



\*Medical school mantra: "When you hear hoof beats, think horses, not zebras." ~ Dr. Theodore Woodward

# OUR PATIENT: SHE NOW PRESENTS TO YOUR OFFICE FOR HELP...

## 10-Minute NASA Lean Test:

Supine HR: 88

Supine Blood Pressure: 100/64

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Test Ended after 7-minutes with near-syncope

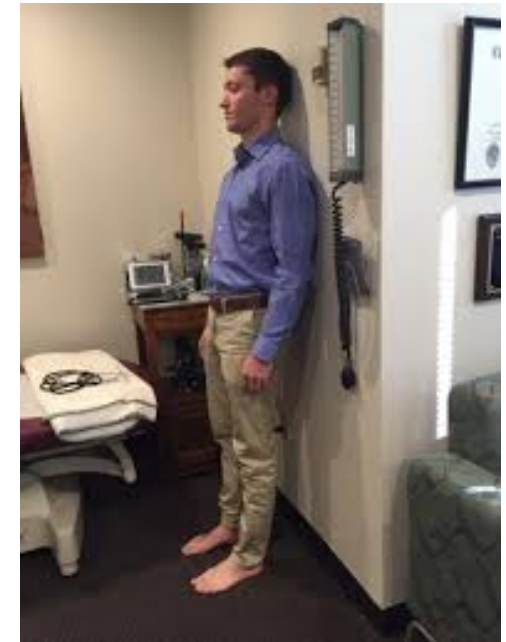
1-minute standing HR: 118

7-minute standing HR: 132

Peak Standing HR: 140 (at 5 minutes)

7-minute blood pressure: 96/78

Pulse Pressure: decreased by 18 mm Hg



## Observers Noted the Following During Testing:

- Cyanosis of the bilateral feet
- Mild rhythmic, “beating” tremor in the neck and RUE, which she believes was similar to her “seizures”

# OUR PATIENT: INCREASING BILATERAL FOOT PAIN AND REDNESS

- Macular, no texture, blanches to touch, warm to touch
- Margins are gradual, not well-demarcated
- Painful, but not pruritic
- No fevers
- No leukocytosis
- Repeat ANA 1:80
- No improvement with a course of antibiotics
- Could this be autoimmune?





# OUR PATIENT: INCREASING BILATERAL FOOT PAIN AND REDNESS

## Skin Biopsy:

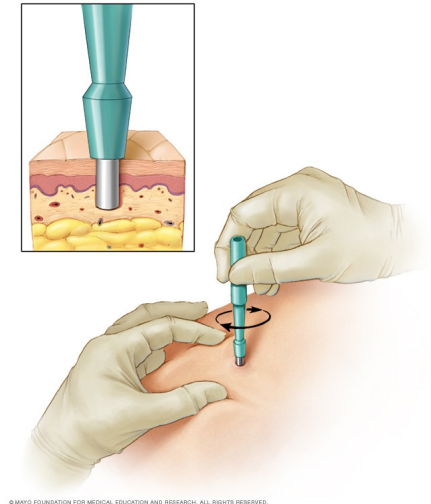
- No particular neutrophilic or lymphocytic infiltration recognized
- No interface dermatitis or positive immunofluorescent stains
- No infectious organisms identified
- Decreased innervation of the skin by small fiber nerves

## Erythromelalgia



# SMALL FIBER POLYNEUROPATHY (SFPN)

- 40% of fibromyalgia patients will have skin biopsies positive for SFPN
- SFPN is not merely associated with pain syndromes, but is often a cause of (or result of) underlying systemic illnesses
- Estimated that 90% of cases of SFPN are undiagnosed and untreated
- Some estimates suggest a worldwide prevalence of 400-500 million people suffering with small fiber neuropathy



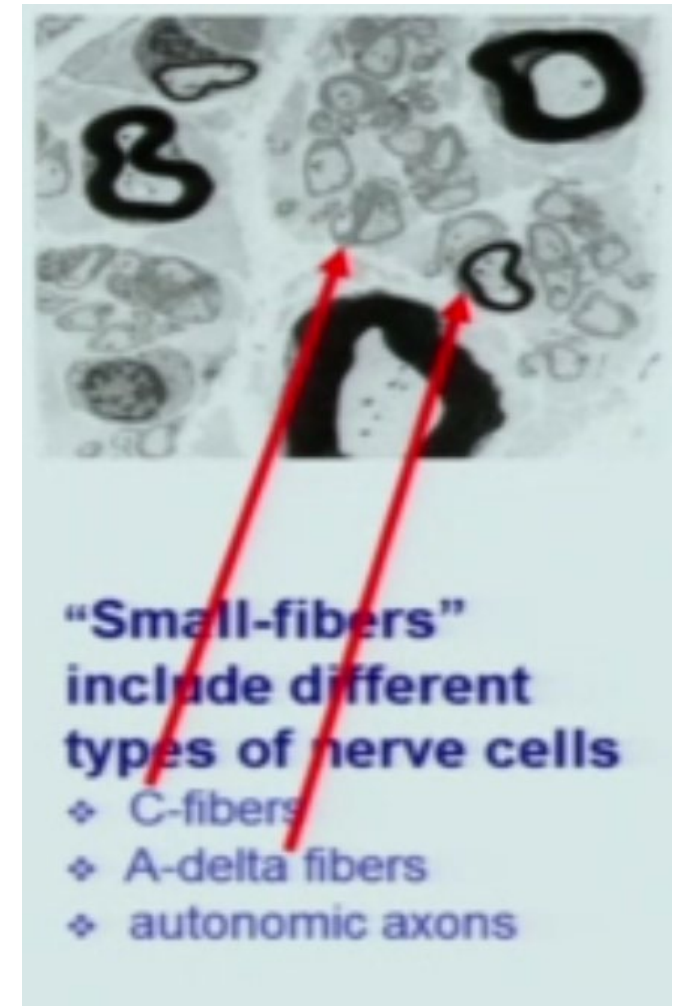
Oaklander AL, Nolano M. Scientific Advances in and Clinical Approaches to Small-Fiber Polyneuropathy: A Review. *JAMA Neurol.* 2019;76(10):1240–1251. doi:10.1001/jamaneurol.2019.2917

# SMALL FIBER POLYNEUROPATHY (SFPN)

## Small Fiber Nerves:

- Small unmyelinated sensory afferent C-fibers
- Thinly myelinated A-delta fibers
- Post-ganglionic, sympathetic autonomic axons

These nerves are small diameter fibers that innervate most organs and tissues

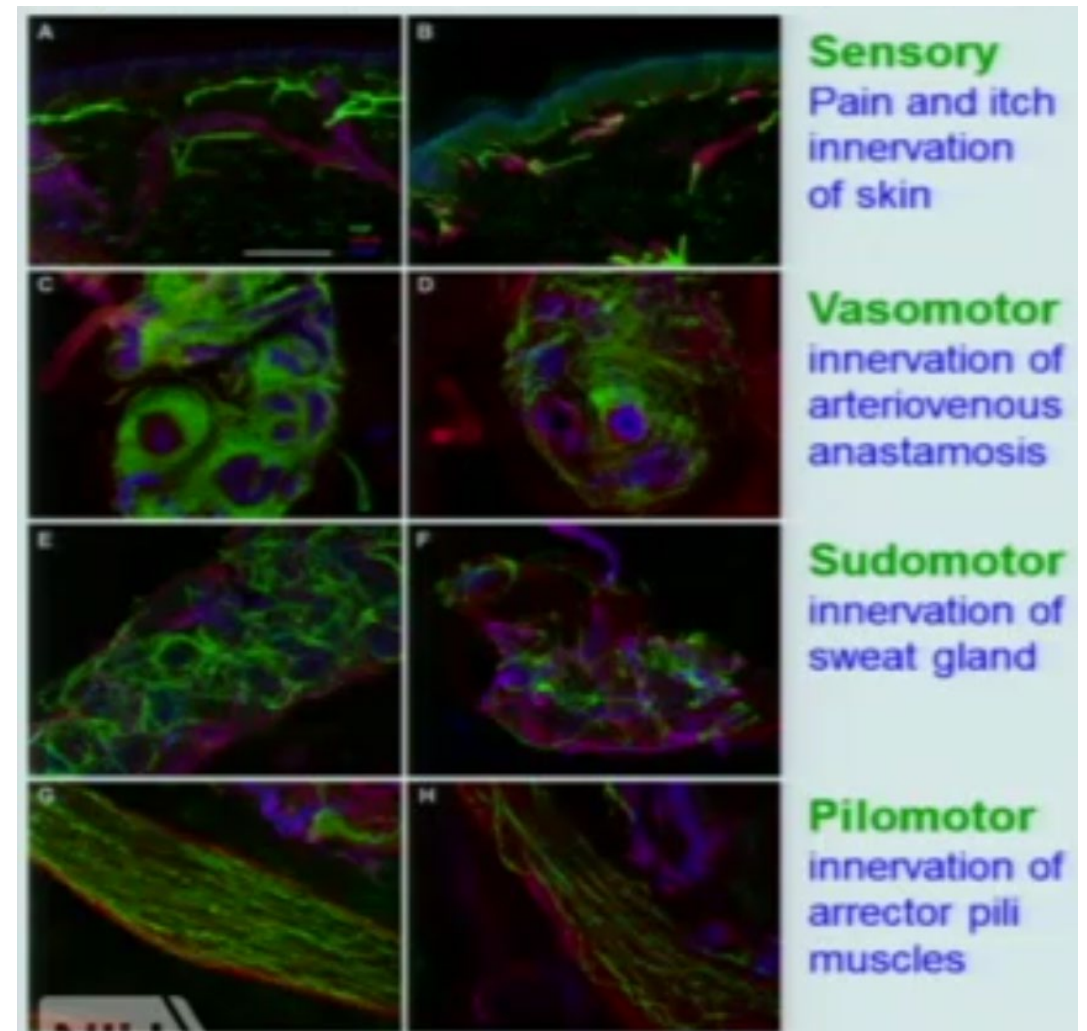


Oaklander AL, Nolano M. Scientific Advances in and Clinical Approaches to Small-Fiber Polyneuropathy: A Review. *JAMA Neurol.* 2019;76(10):1240–1251. doi:10.1001/jamaneurol.2019.2917



# SMALL FIBER POLYNEUROPATHY (SFPN)

Immunofluorescent skin labeling of small fiber nerves



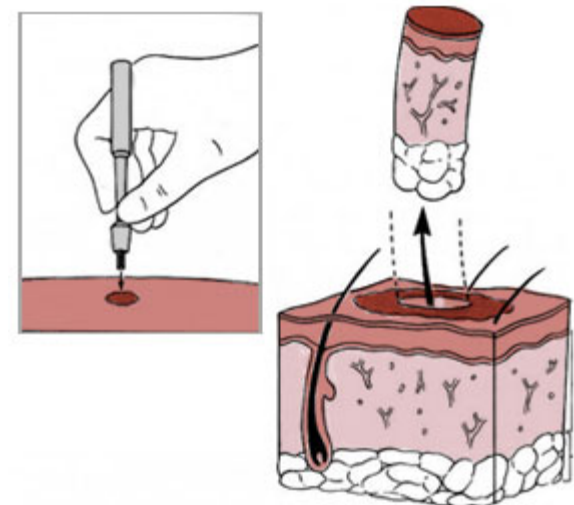
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# SMALL FIBER POLYNEUROPATHY (SFPN)



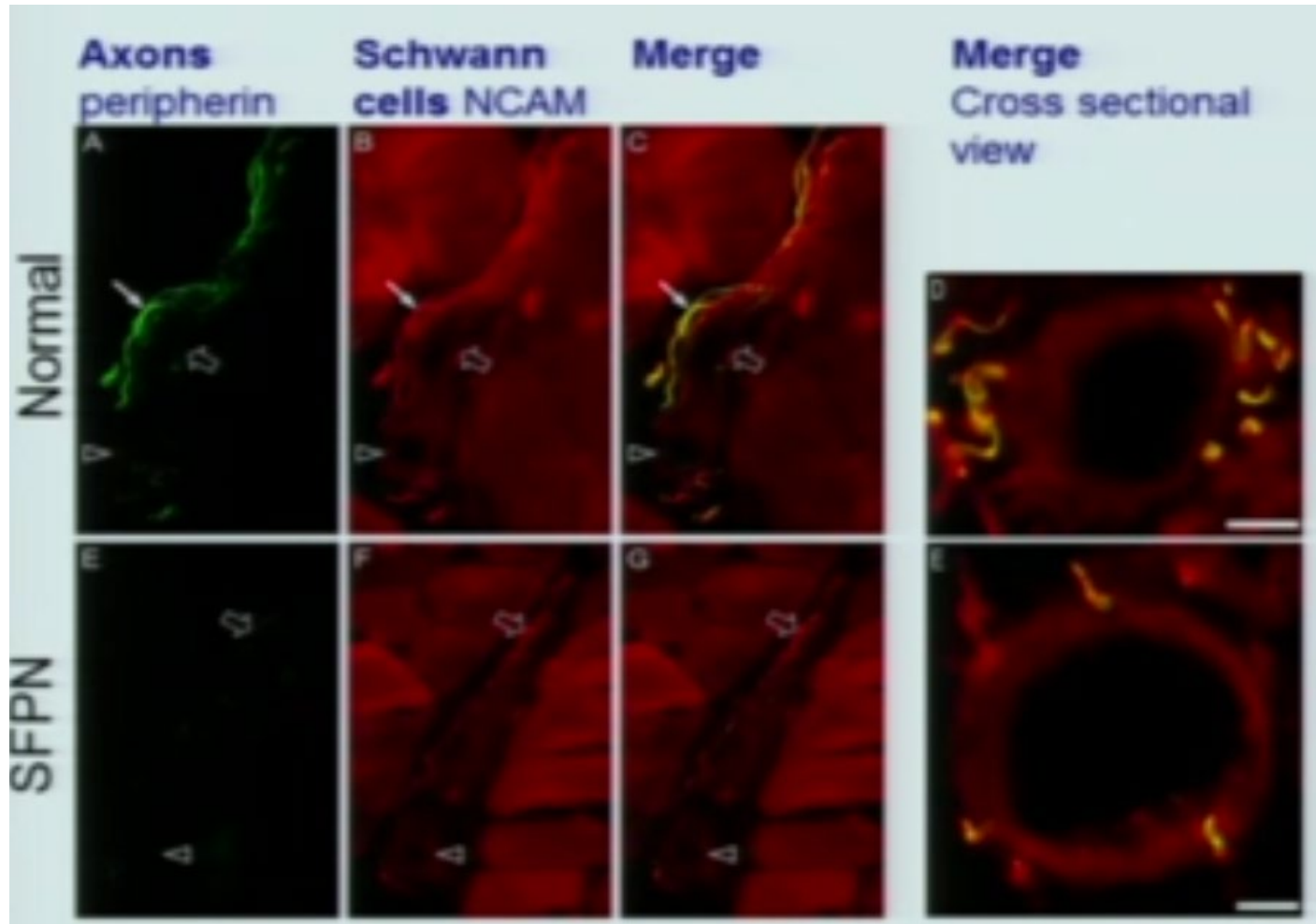
EMG/NCS and formal neurologic exams are not sensitive for the detection of small fiber polyneuropathy

Gold-standard for diagnosis is a 3 mm punch biopsy of the lower leg, as all epidermal nerve fibers are small fibers



Oaklander AL, Nolano M. Scientific Advances in and Clinical Approaches to Small-Fiber Polyneuropathy: A Review. *JAMA Neurol.* 2019;76(10):1240–1251. doi:10.1001/jamaneurol.2019.2917

# SMALL FIBER POLYNEUROPATHY (SFPN)



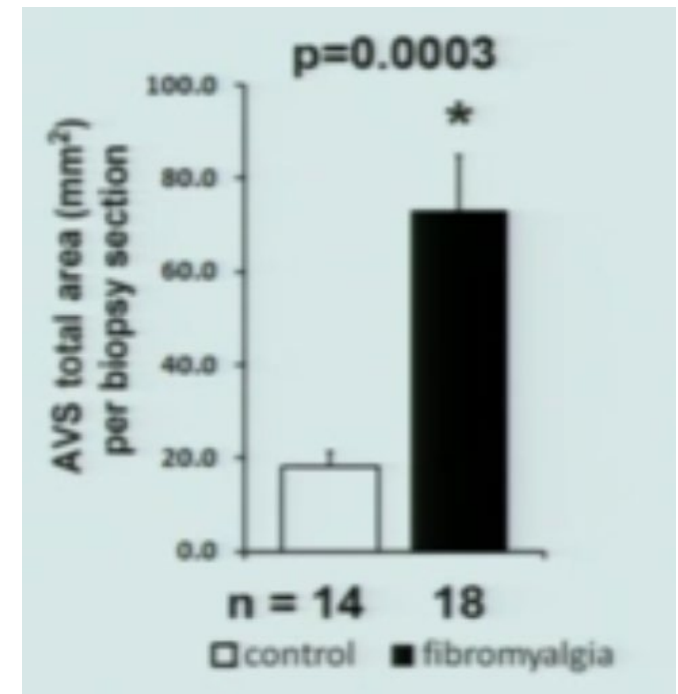
Loss of axon innervation of myovascular structures in small fiber neuropathies

Dori, A., Lopate, G., Keeling, R. and Pestronk, A. (2015), Myovascular innervation: Axon loss in small-fiber neuropathies. *Muscle Nerve*, 51: 514-521. doi:10.1002/mus.24356

# SMALL FIBER POLYNEUROPATHY (SFPN)



- Loss of myovascular innervation can result in vessel patency that leads to arteriovenous shunting of blood
- Capillary beds can be entirely bypassed in this distal “left to right” shunt



Phillip J. Albrecht, PhD, Quanzhi Hou, MD PhD, Charles E. Argoff, MD, James R. Storey, MD, James P. Wymer, MD PhD, Frank L. Rice, PhD, Excessive Peptidergic Sensory Innervation of Cutaneous Arteriole–Venule Shunts (AVS) in the Palmar Glabrous Skin of Fibromyalgia Patients: Implications for Widespread Deep Tissue Pain and Fatigue, *Pain Medicine*, Volume 14, Issue 6, June 2013, Pages 895–915



# SMALL FIBER POLYNEUROPATHY (SFPN)

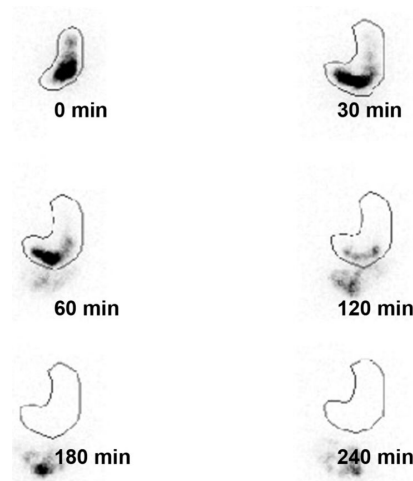
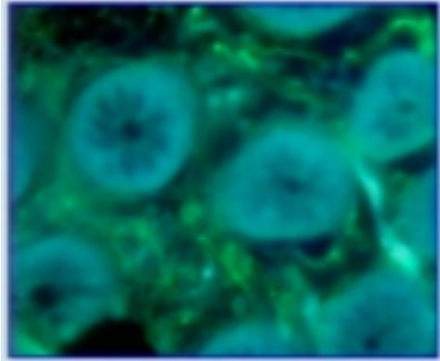
## Autonomic Functions of Small Fiber Nerves:

- Heart rate response to **deep breathing**
- Heart rate and blood pressure response to **Valsalva**
- Heart rate and blood pressure response to **tilt**
- Sudomotor (**sweat**) response
- **Gastrointestinal** functions



Oaklander AL, Nolano M. Scientific Advances in and Clinical Approaches to Small-Fiber Polyneuropathy: A Review. *JAMA Neurol.* 2019;76(10):1240–1251. doi:10.1001/jamaneurol.2019.2917

# SMALL FIBER POLYNEUROPATHY (SFPN)



The gut is densely innervated by small fibers as well, and loss of these fibers can result in wide ranging abdominal and digestive symptoms including:

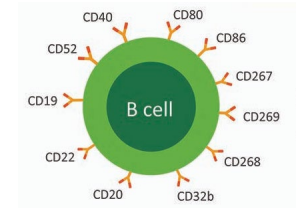


## GI Symptoms of SFPN:

- GI Dysmotility
  - Esophageal Dysmotility
  - Gastric-emptying scintigraphs shows slowed emptying of the stomach
  - Sitz marker studies show alterations of colon transit time
- Post-prandial nausea and vomiting
- GERD
- Weight Loss/Anorexia/Cachexia
- Diarrhea
- Constipation
- Irritable Bowel Syndrome (IBS)

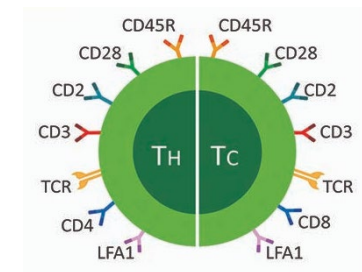
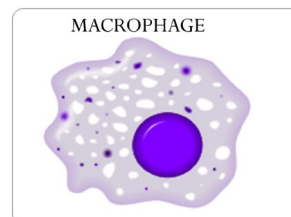
Oaklander AL, Nolano M. Scientific Advances in and Clinical Approaches to Small-Fiber Polyneuropathy: A Review. *JAMA Neurol.* 2019;76(10):1240–1251. doi:10.1001/jamaneurol.2019.2917

# SMALL FIBER POLYNEUROPATHY (SFPN)



## Small Fiber Nerves and the Immune System:

- Most peripheral nervous system structures are shielded from their environments and protected by the blood-nerve and blood-brain barrier
- Small fibers are designed to be exposed to the environment so that they can relay information from that environment to the rest of the “protected” nervous system
- C-fiber nerve ends within the skin respond to external threats through detection of cytokines, interleukins, and other immune/inflammatory signals with an afferent upstream signal
- Neurons in sensory ganglia (like the DRG) are imbued with fenestrated capillaries that help detect infection or inflammation



Oaklander AL, Nolano M. Scientific Advances in and Clinical Approaches to Small-Fiber Polyneuropathy: A Review. *JAMA Neurol.* 2019;76(10):1240–1251. doi:10.1001/jamaneurol.2019.2917



# OUR PATIENT:

## BUT WHAT ABOUT MY HEADACHES?

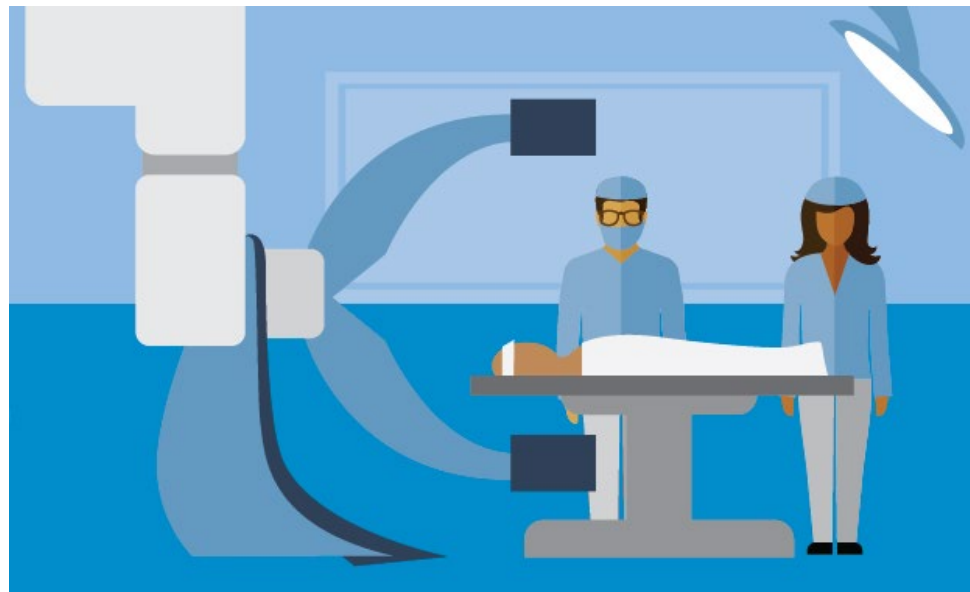
- Long-standing history of migraine headaches since menarche
- Previous frequency of 6 per month
- Frequency now increased to 3-4 per week in the last 1.5 years
- Unclear if aura, often preceded by “fuzzy” vision,
- Associated photophobia, significant sound sensitivity
- Disabling, unable to drive, take care of family or children, prepare food
- Would go to bed and “wait it out”



# OUR PATIENT:

## BUT WHAT ABOUT MY HEADACHES?

- Rizatriptan sometimes would abort headaches, but “underwhelming”
- No benefit with naproxen/caffeine
- Unable to tolerate amitriptyline due to “dizziness”
- No hx of TBI, concussion
- MRI unremarkable, normal neurology exam
- Past trial of topiramate led to difficulty breathing and cognitive slowing
- Could not afford trial of botox therapy





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# MIGRAINE

- Affects up to 15-20% of the adult population
- Migraine is included in the WHO list of top 20 conditions leading to years lived with disability

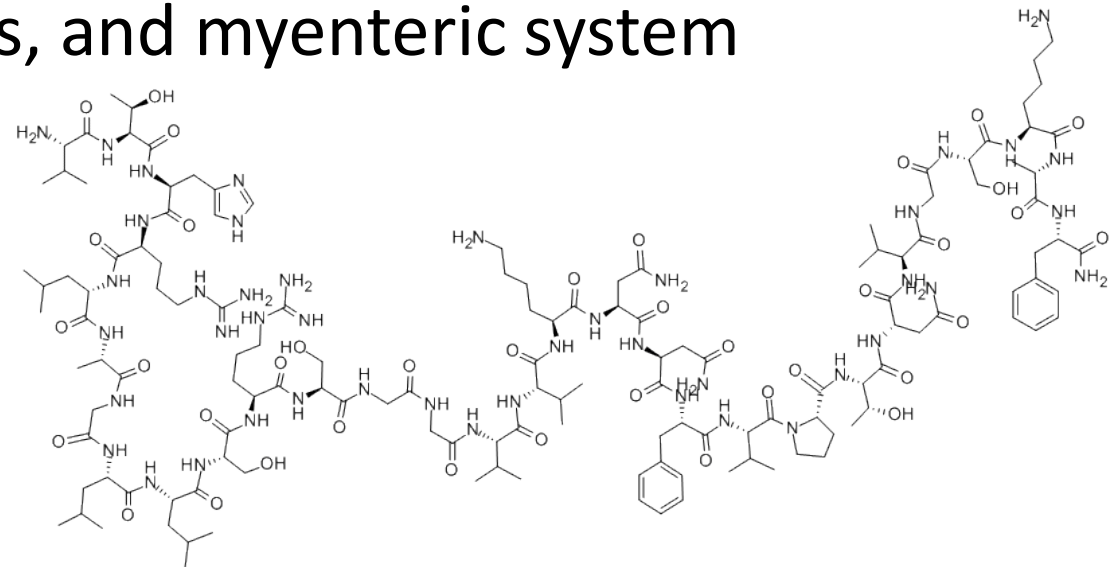
## Calcitonin Gene Related Peptide (CGRP)

- Blood and saliva levels of CGRP are elevated during a migraine attack within migraineurs
- Injection of CGRP can induce a delayed onset migraine in migraineurs but not in healthy controls
- Triptans have been shown to normalize CGRP levels

Torchio, Federica. "The role of CGRP and its Antagonists in Migraine." <http://flipper.diff.org/app/items/info/5242>. 02 Oct. 2013.

# CALCITONIN GENE RELATED PEPTIDE (CGRP)

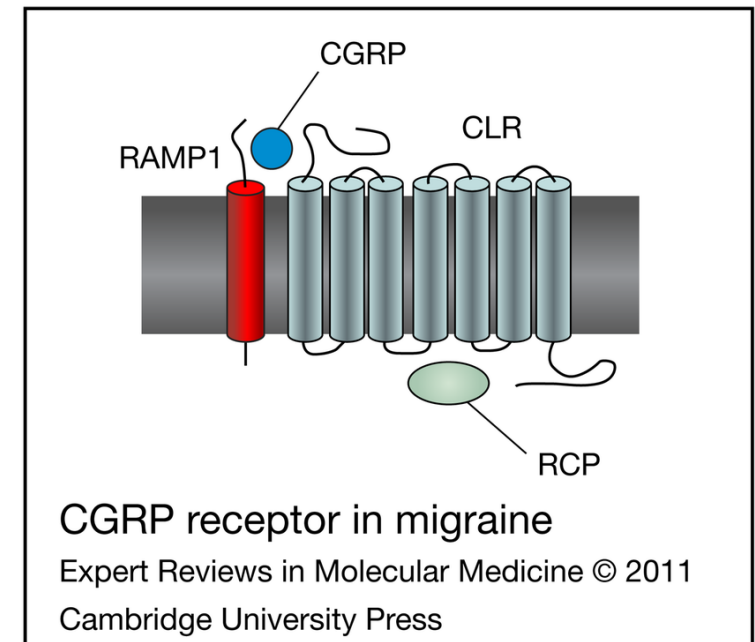
- 37 amino acid neuropeptide
- Most abundantly expressed in sensory neurons
- Primarily functions as a primary afferent neurotransmitter
- Highest concentrations have been found in the of the outer laminae of the spinal cord dorsal horn and within the trigeminal nucleus caudalis (TNC)
- Also found in peripheral fibers innervating the heart, coronary arteries, vascular beds, and myenteric system



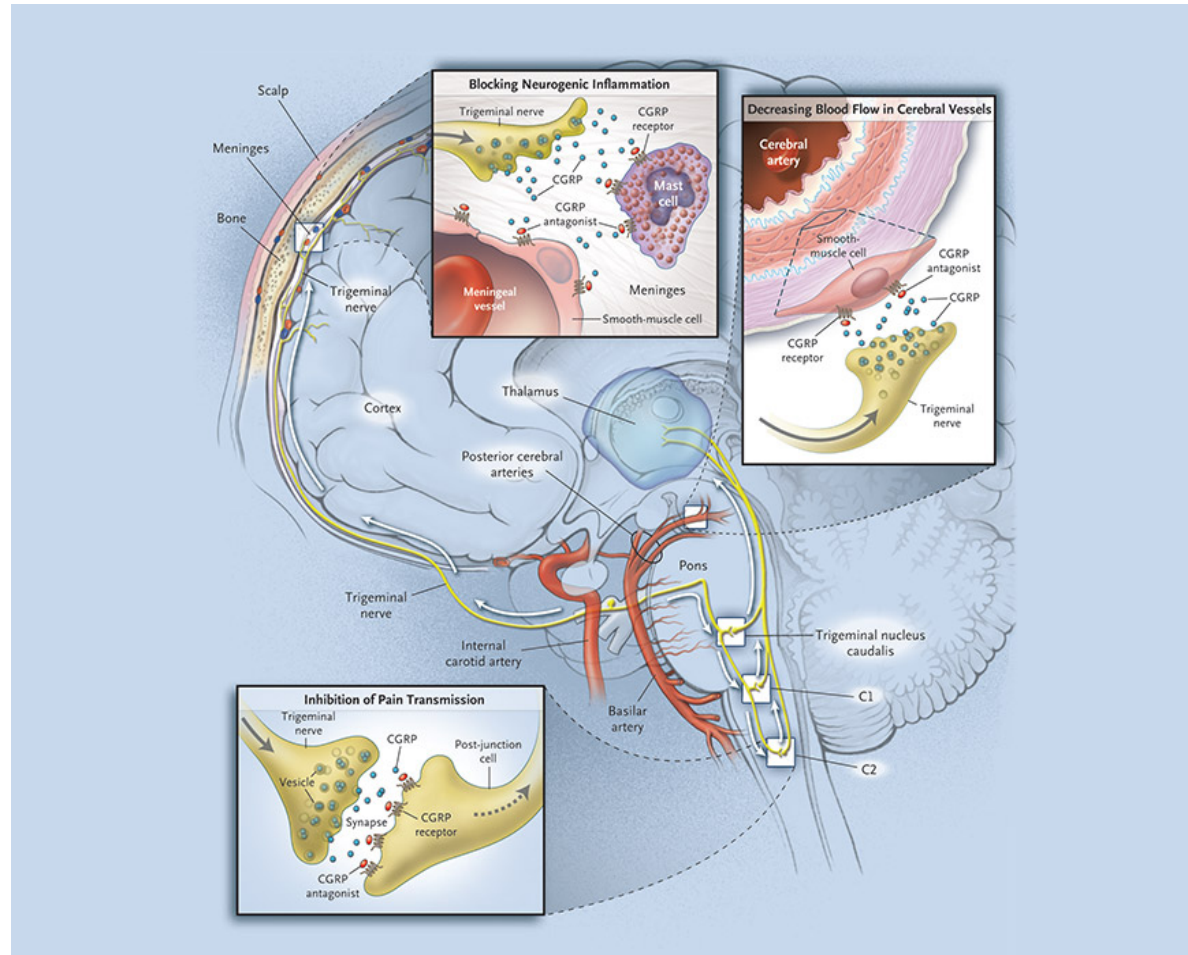
Iyengar S, Ossipov MH, Johnson KW. The role of calcitonin gene-related peptide in peripheral and central pain mechanisms including migraine. *Pain*. 2017;158(4):543–559.

# CGRP RECEPTORS

- Often found on second-order neurons, with very little expression of the receptor upon the cells that actually release CGRP
- Highly concentrated on neurons within the spinal cord and cerebral gray matter
- Highly expressed in the meningeal vasculature, which is innervated by primary afferent fibers from the trigeminal ganglion that release CGRP
- Found upon satellite glial cells and astrocytes as well



# TRIGEMINOVASCULAR SYSTEM – CGRP DEPENDENT



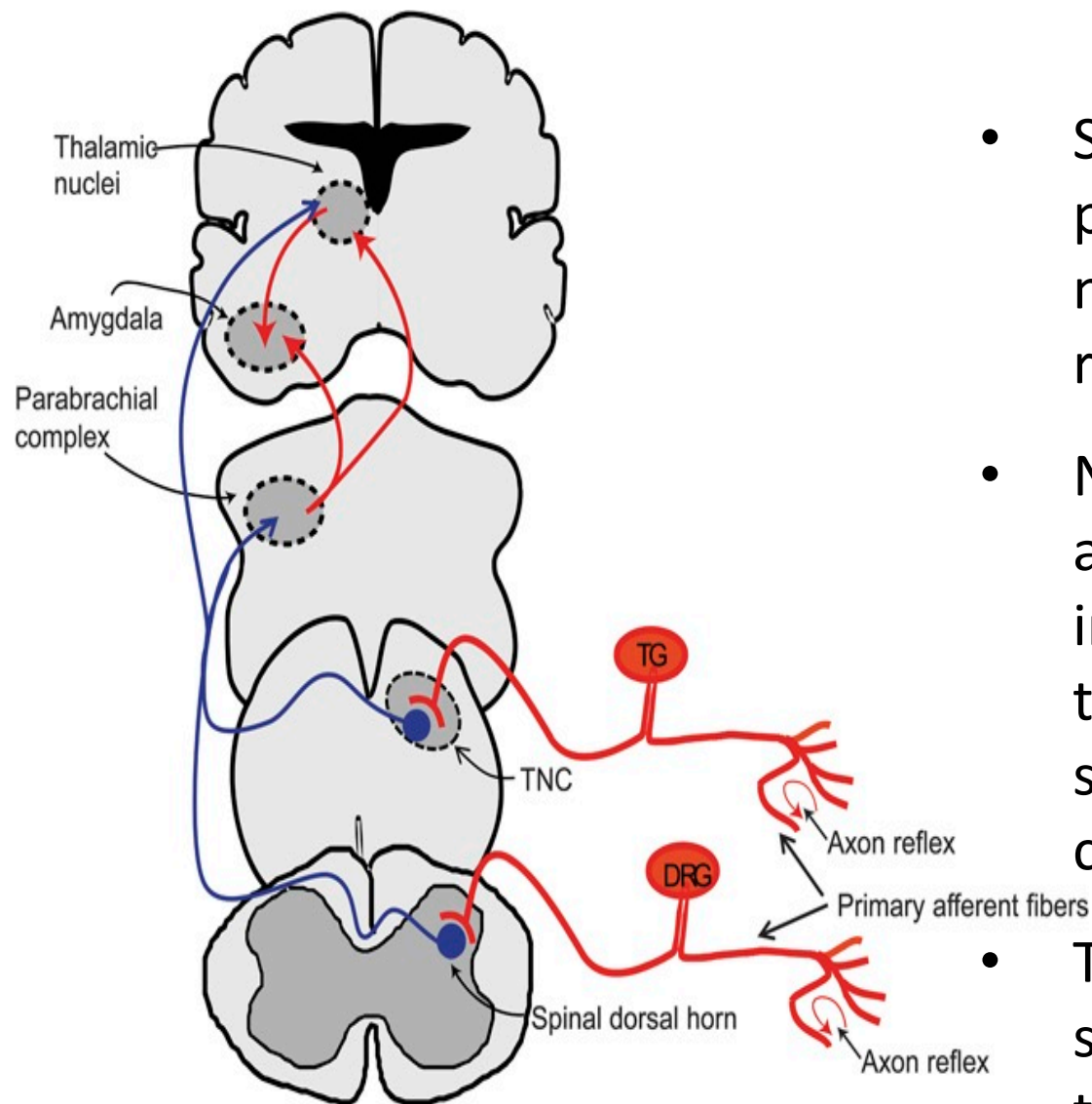
- Neurological system that processes incoming nociceptive signals
- Peripheral inputs originate from meningeal blood vessels to the trigeminal ganglion (most applicable in migraine) or from dorsal root ganglion inputs into the spinal cord
- These inputs are ultimately related to the trigeminal nuclear complex, which includes the trigeminal nucleus caudalis (TNC) and related extensions to the C1-C2 levels

From N Engl J Med, Durham PL, CGRP-Receptor Antagonists — A Fresh Approach to Migraine Therapy? 350:1073-1075, Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

CGRP and the Trigeminal System in Migraine. Iyengar S, Johnson KW, Ossipov MH, Aurora SK. Headache. 2019 May;59(5):659-681.



# PAIN PATHWAYS INVOLVING CGRP



- Stimulation of peripheral sensory nerve pathways utilizing CGRP (red) transmit nociceptive inputs through the dorsal root ganglion (DRG)
- Neurogenic signaling from these primary afferent fibers signaling peripheral inflammation or other noxious stimuli are transmitted to second order neurons in the spinal dorsal horns and trigeminal nucleus caudalis (TNC) within the brainstem
- These signals then propagate into supraspinal sites within the brain including the parabrachial complex, amygdala, and intralaminar thalamic complex

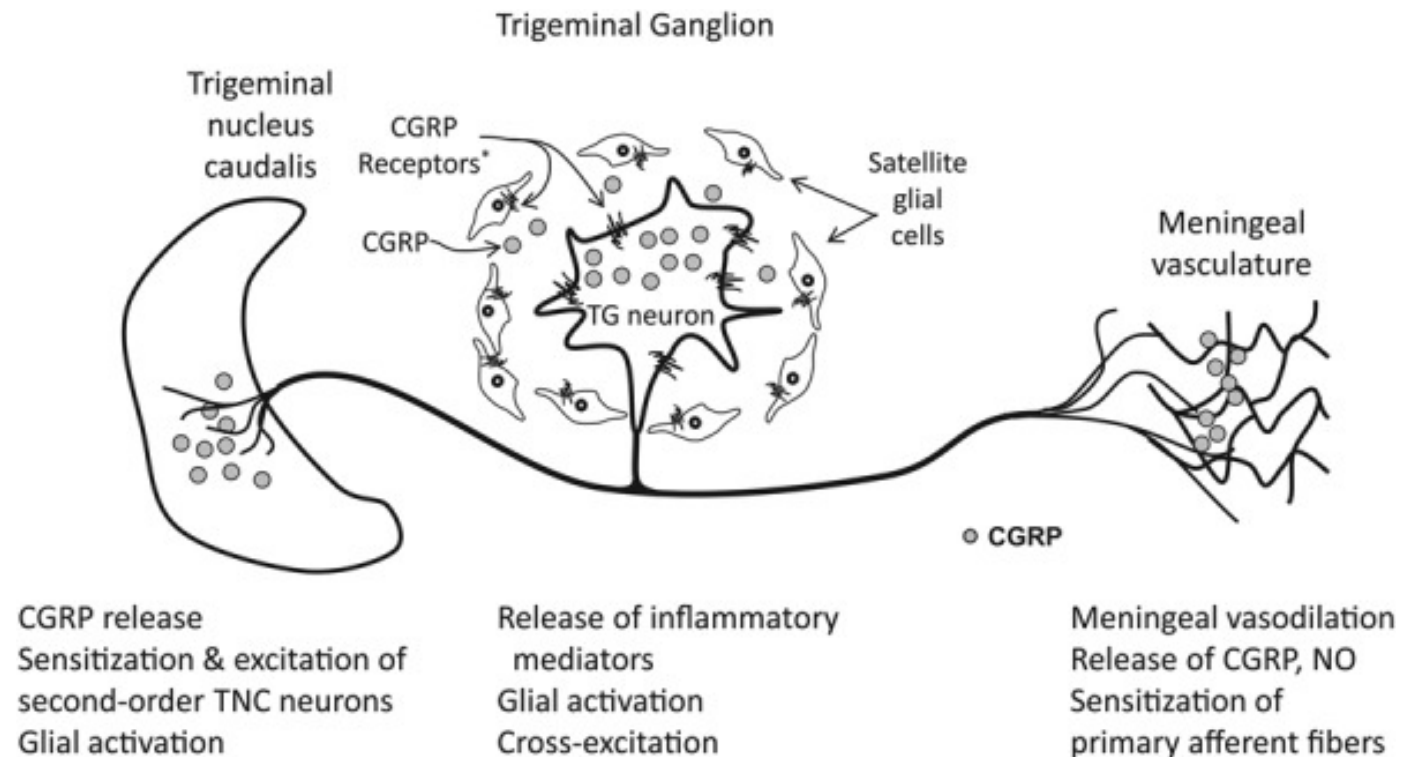
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# PAIN PATHWAYS INVOLVING CGRP

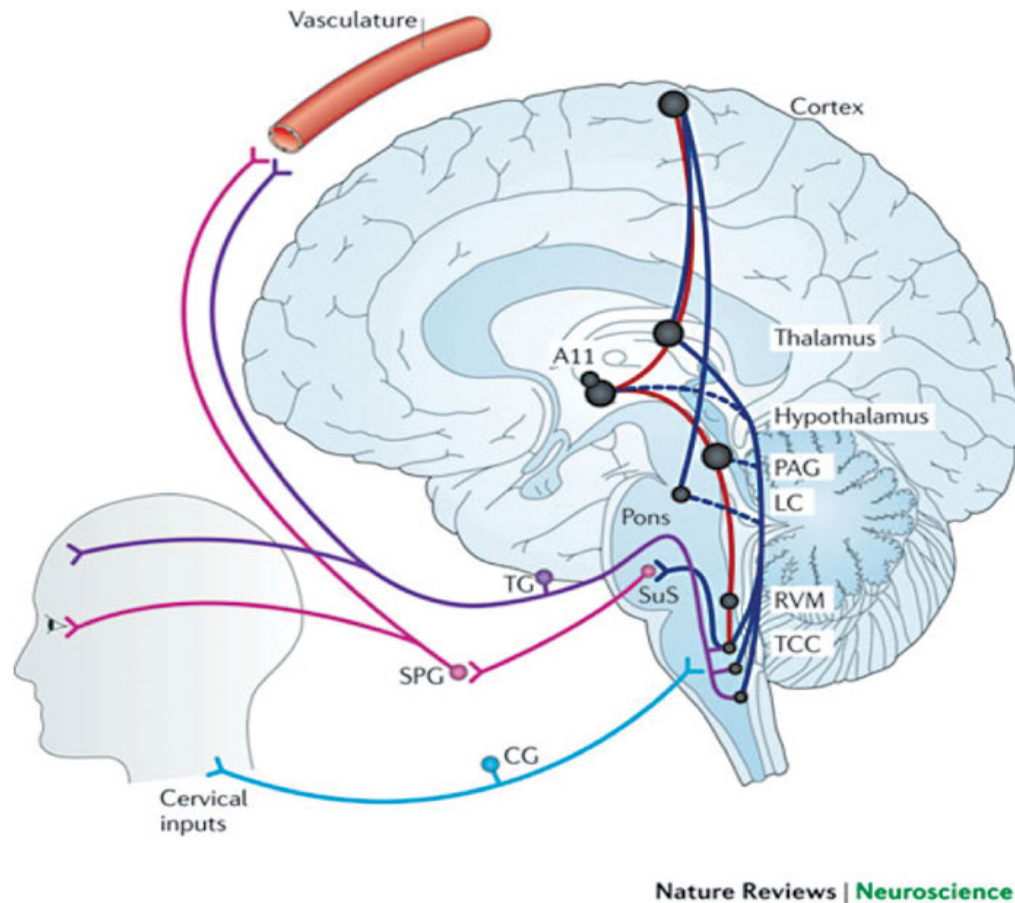
When the trigeminal ganglion receives nociceptive input (ischemia, injury, infection)...

- CGRP is released within the meningeal vasculature to increase vasodilation
- CGRP is released from the TG cell body itself to excite satellite glial cells to release inflammatory mediators
- CGRP released within the TNC leads to excitation of second order neurons within the trigeminovascular system, leading to central sensitization and increased hyperalgesia and allodynia



Iyengar S, Ossipov MH, Johnson KW. The role of calcitonin gene-related peptide in peripheral and central pain mechanisms including migraine. *Pain*. 2017;158(4):543–559.

# TRIGEMINOVASCULAR SYSTEM



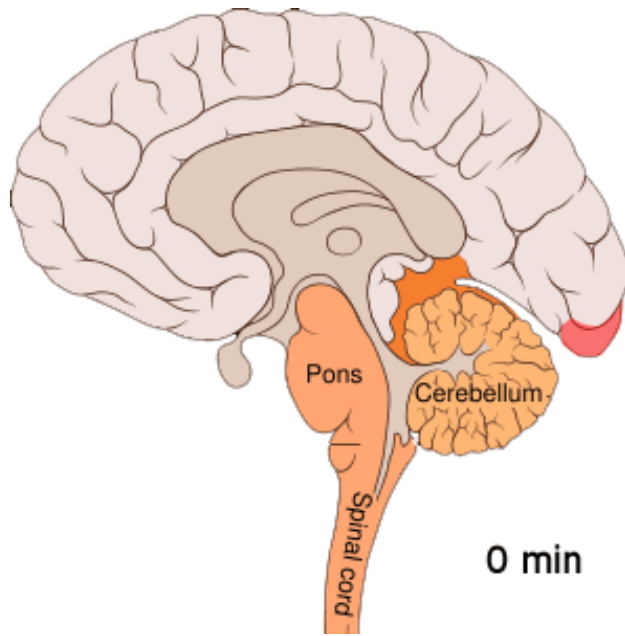
Akerman S, Holland PR, Goadsby PJ. Diencephalic and brainstem mechanisms in migraine. *Nature reviews*. 2011;12:570-84.

- The trigeminal nucleus complex can then transmit activation to second-order neurons within the posterior thalamus, among other locations, further propagating, central sensitization and increased hyperalgesia and allodynia
- There are several other sensory inputs into the trigeminal ganglion and trigeminal nuclear complex that may participate in activating the trigeminovascular reflex as well

CGRP and the Trigeminal System in Migraine. Iyengar S, Johnson KW, Ossipov MH, Aurora SK. *Headache*. 2019 May;59(5):659-681.

# MIGRAINE TRIGGER?

## CORTICAL SPREADING DEPRESSION



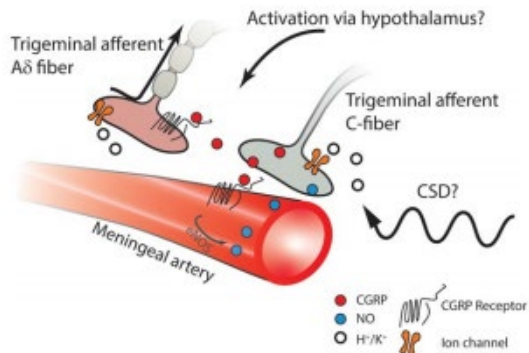
By User:S. JähnichenBrain\_bulbar\_region.svg: Image:Brain human sagittal section.svg by Patrick J. Lynch; Image:Brain bulbar region.PNG by DO11.10; present image by Fvasconcellos. - Brain\_bulbar\_region.svg, CC BY 2.5, <https://commons.wikimedia.org/w/index.php?curid=6049291>

R. Suzanne Zukin, Teresa Jover, Hidenori Yokota, Agata Calderone, Monica Simionescu, C. Geoff Lau, Chapter 42 - Molecular and Cellular Mechanisms of Ischemia-Induced Neuronal Death, Editor(s): J.P. Mohr, Dennis W. Choi, James C. Grotta, Bryce Weir, Philip A. Wolf, Stroke (Fourth Edition), Churchill Livingstone, 2004, Pages 829-854.

CGRP and the Trigeminal System in Migraine.  
Iyengar S, Johnson KW, Ossipov MH, Aurora SK.  
Headache. 2019 May;59(5):659-681.

- A wave of sustained depolarization moving through intact brain tissue
- Triggered by oscillations in hypothalamic or activity or by focal stimulation of the cerebral cortex from insults such as impaired brain metabolism, focal ischemia, or other injurious stimuli
- As brain cells lose energy from these insults, cellular pumps that utilize energy to force ions into and out of a cell begin to fail to maintain a normal concentration gradient
- Redistribution of ions between the intracellular and extracellular environment, with a large rise of extracellular potassium and in glutamate, which initiates and propagates neuronal and glial excitation and hyperactivity
- This is followed by prolonged suppression of neuronal activity, reduction in extracellular space, and local tissue edema

# CORTICAL SPREADING DEPRESSION AND THE TRIGEMINOVASCULAR SYSTEM



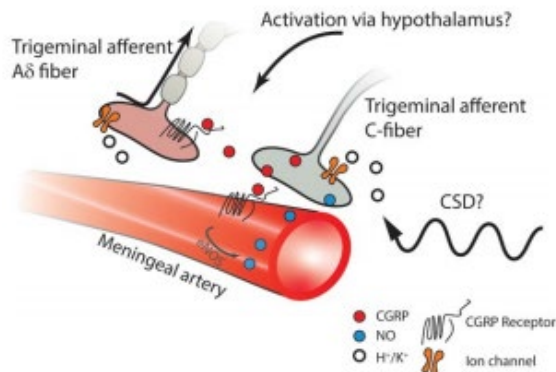
- In migraineurs, cortical brain cells express upregulation of genes involved in inflammatory processing (COX-2, TNF-alpha, IL-1Beta, galanin, and metalloproteinases, etc.)
- Repeated inflammatory molecules release from cortical cells during CSD leads to increased permeability of the blood-brain barrier
- Secondary release of other intracellular molecules and ions that **sensitize**:
  - A.) Propagation of subcortical spreading depression
  - B.) Dural nociceptors of the trigeminovascular system
- CSD is also associated with an increase in cerebral vasoconstrictive tone
- Both an increase in proinflammatory substances and in vasoconstriction can be sensed by trigeminal sensory C-fiber nerve endings

CGRP and the Trigeminal System in Migraine. Iyengar S, Johnson KW, Ossipov MH, Aurora SK. Headache. 2019 May;59(5):659-681.

David Borsook, Nasim Maleki, Rami Burstein, Chapter 42 - Migraine, Editor(s): Michael J. Zigmond, Lewis P. Rowland, Joseph T. Coyle, Neurobiology of Brain Disorders, Academic Press, 2015, Pages 693-708

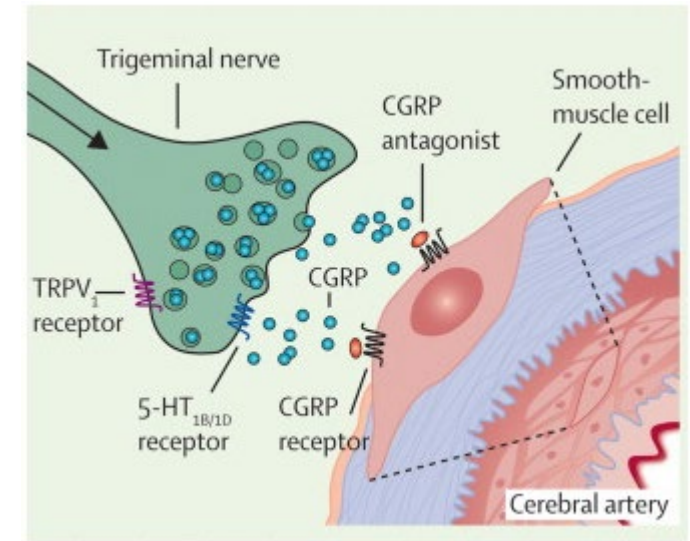


# TRIGEMINOVASCULAR ACTIVATION

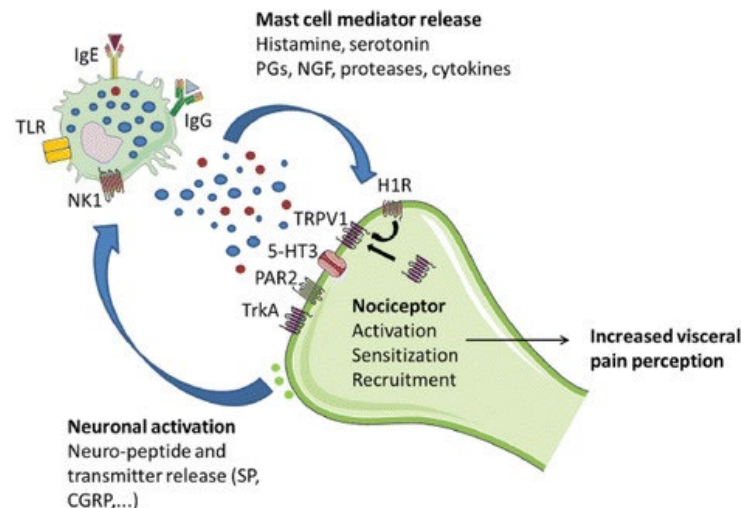


- Sensory C-fibers respond to these triggers with the release CGRP
- CGRP receptors are located upon the **meningeal vasculature** and upon trigeminal afferent **A-delta fibers**, upon local **dural mast cells**, and upon **satelite cells**

- CGRP-activated dural mast cells create an inflammatory milieu that further activates nociceptor stimulation of both CGRP and non-CGRP-related pathways



- CGRP acting upon smooth muscle cells of the meningeal vasculature incites intense compensatory nitric oxide-driven cerebral vasodilation

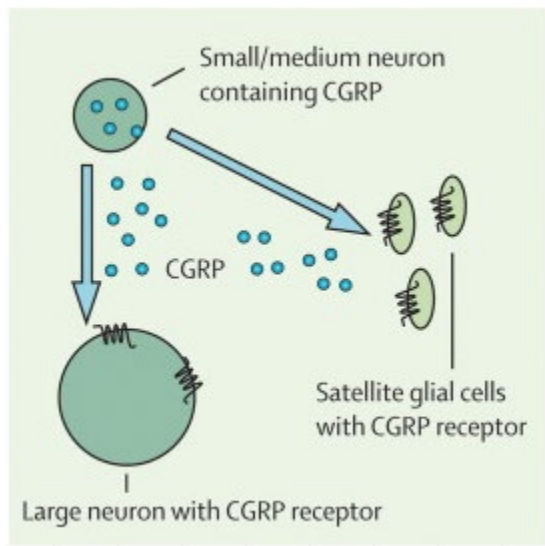


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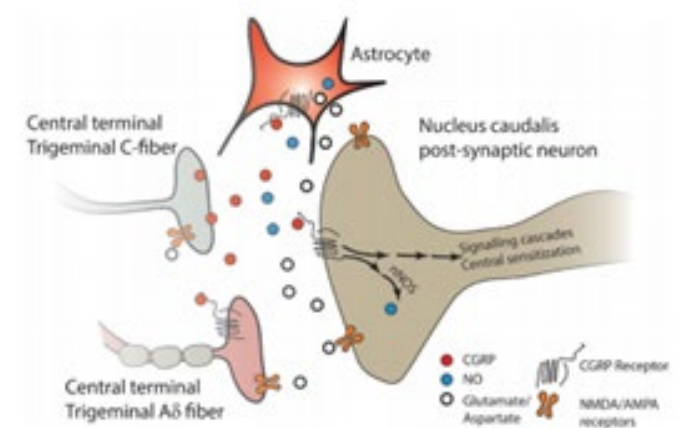
Chumpitazi, Bruno & Shulman, Robert. (2016). Underlying molecular and cellular mechanisms in childhood irritable bowel syndrome. Molecular and cellular pediatrics. 3. 11. 10.1186/s40348-016-0036-8.

Torchio, Federica. "The role of CGRP and its Antagonists in Migraine." <http://flipper.diff.org/app/items/info/5242>. 02 Oct. 2013.

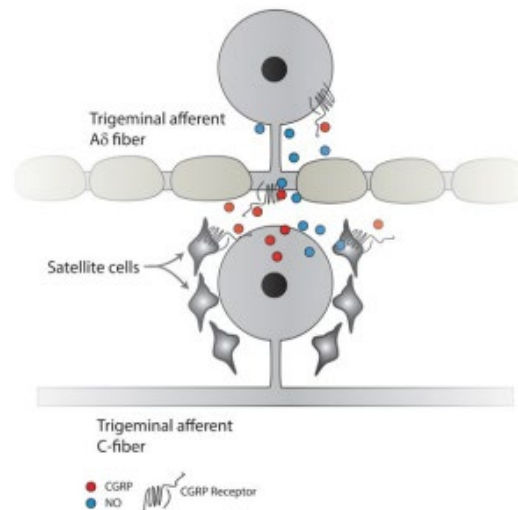
# TRIGEMINOVASCULAR ACTIVATION



- CGRP can also diffuse to satellite glial cells and astrocytes, which then release more nitric oxide and other inflammatory mediations



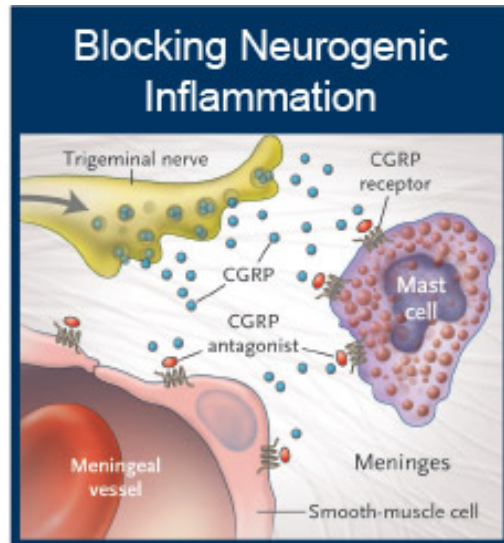
- CGRP and nitric oxide acting upon trigeminal A-delta fibers result in their **sensitization** and downstream activation of the trigeminal nucleus caudalis (TNC) and second-order neuron activation



- This additional nitric oxide release of inflammatory mediators may then act upon nearby neurons without CGRP receptors
- Cascade ultimately promotes release of other excitatory substances within other second-order neural networks and promotes long-term central sensitization

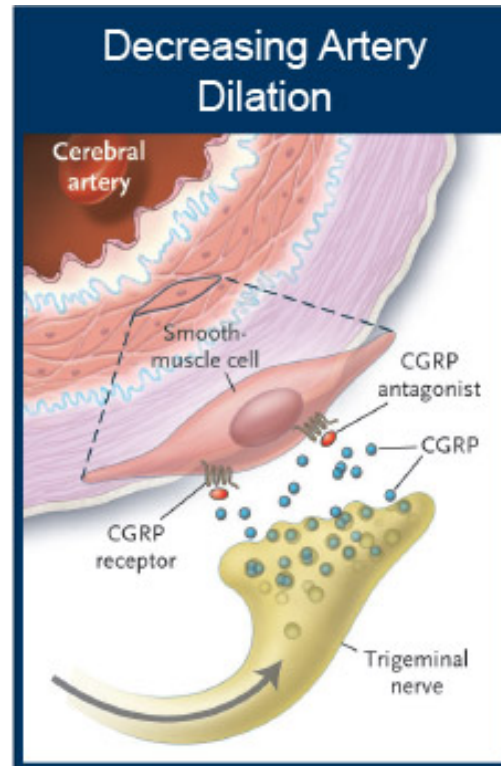
CGRP and the Trigeminal System in Migraine. Iyengar S, Johnson KW, Ossipov MH, Aurora SK. Headache. 2019 May;59(5):659-681.

# CGRP ANTAGONISTS

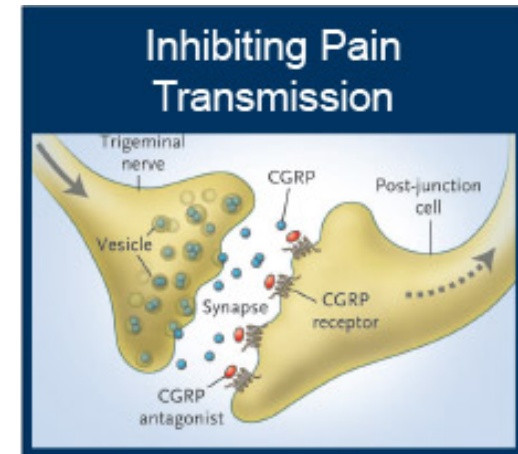


- 1 Binding of CGRP receptor antagonists (red) to receptors located on mast cells inhibits inflammation caused by trigeminal release of CGRP (blue) onto mast cells within the outer covering of the brain (meninges)

From N Engl J Med, Durham PL, CGRP-Receptor Antagonists — A Fresh Approach to Migraine Therapy? 350:1073-1075, Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.



- 2 CGRP receptor antagonists (red) inhibit dilation of arteries induced by trigeminal nerve CGRP (blue) by blocking CGRP receptors located on smooth muscle cells within vessel walls (without the unwanted effect of active vasoconstriction)



- 3 CGRP receptor antagonist (red) binding to receptors located on the post-junctional cell suppresses CGRP-induced (blue) enhancement of trigeminal nerve pain signals coming from the periphery to the brain (trigeminal nucleus caudalis (TNC))

From N Engl J Med, Durham PL, CGRP-Receptor Antagonists — A Fresh Approach to Migraine Therapy? 350:1073-1075, Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.



EMERGING EVIDENCE SUGGESTS THAT DYSFUNCTIONAL PAIN STATES, SUCH AS OSTEOARTHRITIS, VISCERAL PAIN HYPERSENSITIVITY SYNDROMES, FIBROMYALGIA, INFLAMMATORY BOWEL SYNDROME, NEUROPATHIC PAIN, AND HEADACHES, INCLUDING MIGRAINE HEADACHE, MAY BE CAUSED IN PART BY A DEFICIENT ENDOGENOUS PAIN INHIBITORY SYSTEM THAT ALLOWS THE DEVELOPMENT OF CENTRAL SENSITIZATION.

Iyengar S, Ossipov MH, Johnson KW. The role of calcitonin gene-related peptide in peripheral and central pain mechanisms including migraine. *Pain*. 2017;158(4):543–559.

# OUR PATIENT:

## DEVELOPING NEW “ALLERGIES”

- Started spending time outside in the back yard with her dog and kids
- Noting she was getting transient rashes on her arms, chest, neck, face, and back with sun exposure
- Rashes would last for 2-3 hours and then resolve
- Rashes were pruritic
- ANA: 1:80 (homogenous)
- No new meds or supplements
- Tried using sunscreen and staying in the shade the next time she went outside, but still broke out similar rashes



No longer able to eat asparagus, would feel very nauseated, experienced chest palpitations, and noted a rash on the back of her left hand

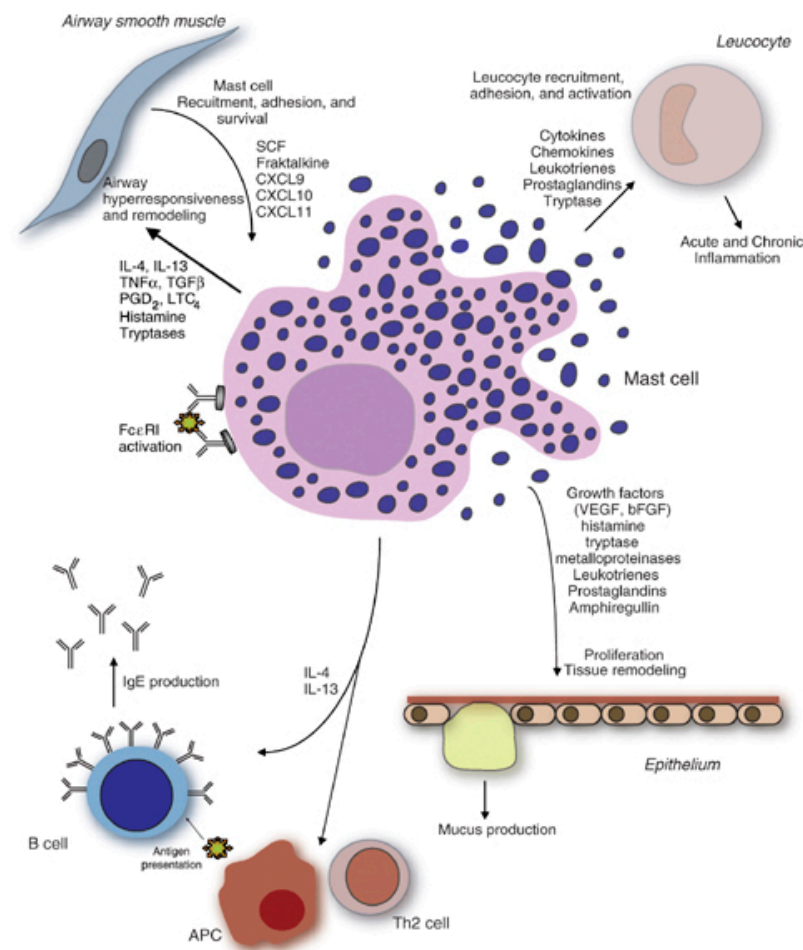
- Hands would become swollen and painful when folding family laundry and she would experience increasing rhinorrhea, dyspnea, wheezing
- No hx of hereditary angioedema or anaphylaxis
- No hx of ACEI or ARB exposure



© Can Stock Photo

# MAST CELL ACTIVATION

- “Inappropriate” or “Defective” mast cells activate, degranulate, and release their inflammatory mediators as a result of abnormal triggering signals
- Syndrome itself is classified by episodic symptoms consistent with mast cell mediator release and affecting two or more organ systems
- These episodes are idiopathic and are not known to be caused by IgE antibody or other allergic triggers known to activate mast cells
- Symptoms should decrease in frequency, severity, or resolve with anti-mediator therapies such as antihistamines, anti-leukotriene therapies, or mast cell stabilization therapies

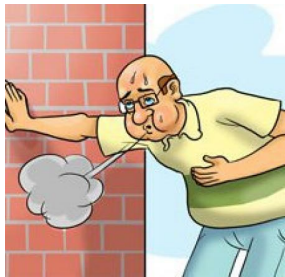


Clinical & Experimental Allergy, Volume: 38, Issue: 1, Pages: 4-18, First published: 21 November 2007, DOI: (10.1111/j.1365-2222.2007.02886.x)

Mast Cell Activation Syndrome: A review. Frieri M., Patel R., Celestin J. Curr Allergy Asthma Rep. 2013 Feb;13(1):27-32. doi: 10.1007/s11882-012-0322-z.

“Mast Cell Activation Syndrome: AAAAI.” *The American Academy of Allergy, Asthma, & Immunology*, [www.aaaai.org/conditions-and-treatments/related-conditions/mcas](http://www.aaaai.org/conditions-and-treatments/related-conditions/mcas)

# MAST CELL ACTIVATION



“Symptoms and Triggers of Mast Cell Activation - TMS - The Mastocytosis Society.” *The Mastocytosis Society*, 29 July 2019, [tmsforacure.org/symptoms/symptoms-and-triggers-of-mast-cell-activation/](https://tmsforacure.org/symptoms/symptoms-and-triggers-of-mast-cell-activation/).

## MAST CELL MEDIATOR SYMPTOMS

### Anaphylaxis

Flushing of the face, neck, and chest

Itching, +/- rash

Hives, skin rashes

Angioedema (swelling)

Nasal itching and congestion

Wheezing and shortness of breath

Throat itching and swelling

Headache and/or brain fog, cognitive dysfunction, anxiety, depression

Diarrhea, nausea, vomiting, abdominal pain, bloating, gastroesophageal reflux disease (GERD)

Bone/muscle pain, osteosclerosis, osteopenia, osteoporosis

Light-headedness, syncope/fainting

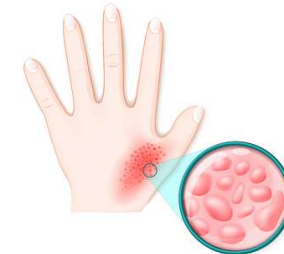
Rapid heart rate, chest pain

Low blood pressure, high blood pressure at the start of a reaction, blood pressure instability

Uterine cramps or bleeding



### HIVES



UNEXPLAINED  
DIZZINESS

# MAST CELL ACTIVATION

Table 1. Possible Effects of Some Mast Cell Mediators<sup>13, 14</sup>

MEDIATOR	POSSIBLE EFFECTS
Histamine	Flushing, itching, diarrhea, hypotension
Leukotrienes	Shortness of breath
Prostaglandins	Flushing, bone pain, brain fog, cramping
Tryptase	Osteoporosis, skin lesions
Interleukins	Fatigue, weight loss, enlarged lymph nodes
Heparin	Osteoporosis, problems with clotting/bleeding
Tumor Necrosis Factor- $\alpha$	Fatigue, headaches, body aches

This list is by no means complete and serves as an example. Mast cells secrete many mediators responsible for numerous symptoms within different organ systems.

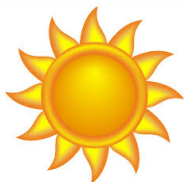
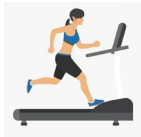
“Symptoms and Triggers of Mast Cell Activation - TMS - The Mastocytosis Society.” *The Mastocytosis Society*, 29 July 2019, [tmsforacure.org/symptoms/symptoms-and-triggers-of-mast-cell-activation/](https://tmsforacure.org/symptoms/symptoms-and-triggers-of-mast-cell-activation/).



# MAST CELL ACTIVATION TRIGGERS

Figure 1. Some *Potential* Mast Cell Triggers<sup>2-5</sup>

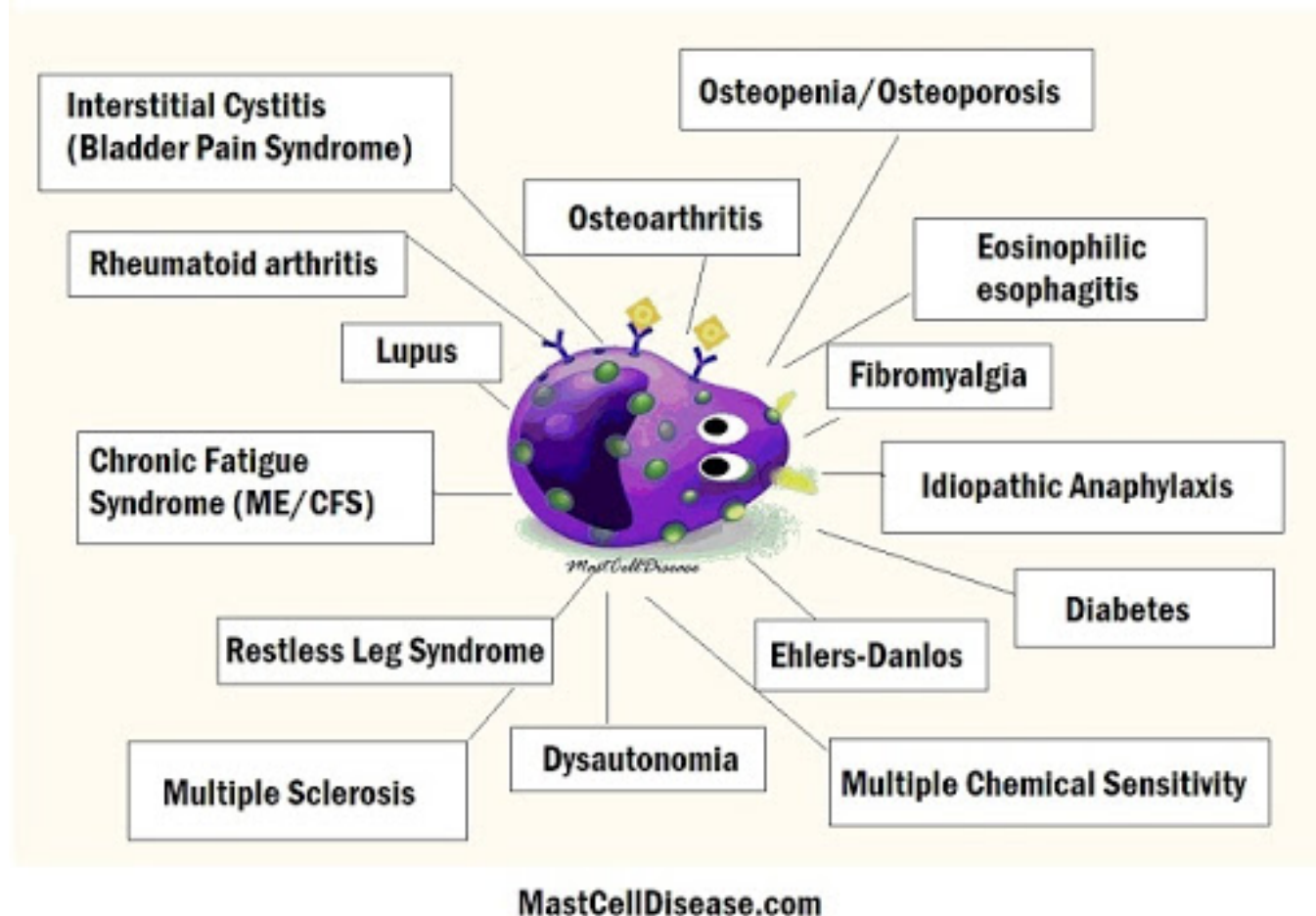
- Heat, cold or sudden temperature changes
- Stress: emotional, physical, including *pain*, or environmental (i.e., weather changes, pollution, pollen, pet dander, etc.)
- Exercise
- Fatigue
- Food or beverages, including alcohol
- Drugs (opioids, NSAIDs, antibiotics and some local anesthetics) and contrast dyes
- Natural odors, chemical odors, perfumes and scents
- Venoms (bee, wasp, mixed vespids, spiders, fire ants, jelly fish, snakes, biting insects, such as flies, mosquitos and fleas, etc.)
- Infections (viral, bacterial or fungal)
- Mechanical irritation, friction, vibration
- Sun/sunlight



“Symptoms and Triggers of Mast Cell Activation - TMS - The Mastocytosis Society.” *The Mastocytosis Society*, 29 July 2019, [tmsforacure.org/symptoms/symptoms-and-triggers-of-mast-cell-activation/](https://tmsforacure.org/symptoms/symptoms-and-triggers-of-mast-cell-activation/).

# MAST CELL ACTIVATION DISEASE ASSOCIATIONS

## Mast Cell Disease Coexisting Conditions



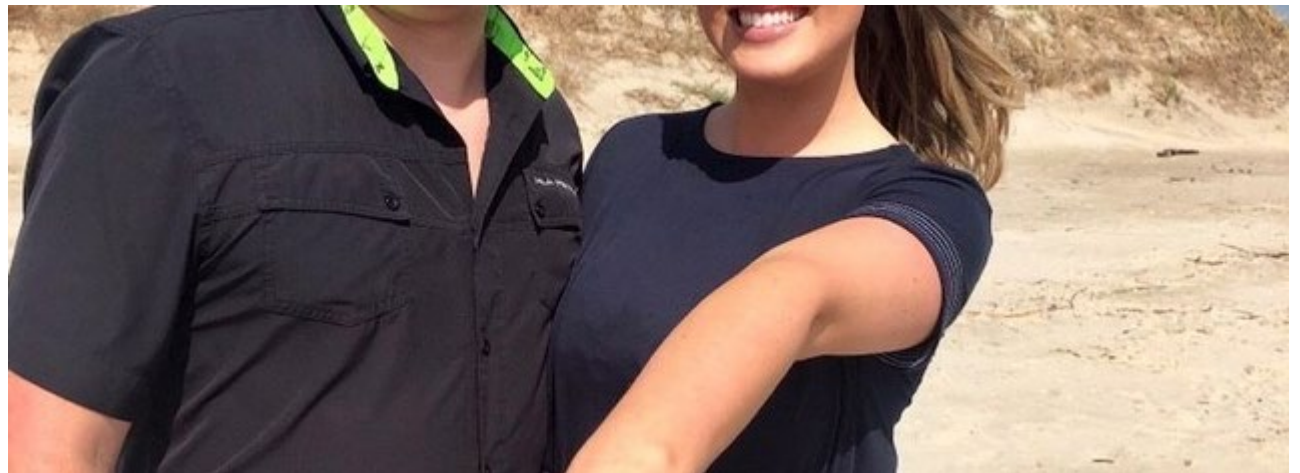
"MCAS." *Clear Health Centers*, 22 Sept. 2019, [www.clearhealthcenters.com/mast-cell-activation-syndrome-utah-physician/](http://www.clearhealthcenters.com/mast-cell-activation-syndrome-utah-physician/).

# OUR PATIENT: FREQUENT “SPRAINED JOINTS” AND JOINT PAIN



- Tried to implement mild exercise and core strengthening with yoga
- Joint “sprains” were becoming frequent and yoga seemed to be exacerbating specific joints like her elbows, knees, wrists

- Pain with movement, use and improved with rest
- No clear joint swelling, erythema, redness
- No response to acetaminophen
- Mild improvement with oral NSAID’s but this would cause dyspepsia
- Has always been “more flexible” than others
- Remembers joint pains and sprains leading her to quit gymnastics as a child



# HYPERMOBILE EHLER'S DANLOS SYNDROME

- Hypermobile-type Ehler's Danlos is the most common subtype of EDS and is thought to be the most common of all hereditary disorders of connective tissue disease
- This diagnosis has replaced the previous classifications for EDS Type III, EDS-HT (hypermobility type), and joint hypermobility syndrome (JHS)
- Prevalence of EDS is as high as 1:5000 people, 80-90% of which is hEDS (10 million people in the USA alone)
- Unlike with classic or vascular EDS, no single gene mutation causing hEDS has been identified
- hEDS is more likely a spectrum disorder with multiple genetic influences
- In general, hEDS is thought to be an autosomal dominant disorder with incomplete penetrance, influenced by age and gender, with symptoms more common in females



Castori, Marco. (2013). Joint hypermobility syndrome (a.k.a. Ehlers-Danlos Syndrome, Hypermobility Type): An updated critique. *Giornale italiano di dermatologia e venereologia : organo ufficiale, Società italiana di dermatologia e sifilografia*. 148. 13-36.

"Hypermobile Ehlers-Danlos Syndrome: Clinical Description and Natural History (for Non-Experts)." *The Ehlers Danlos Society*, 6 Mar. 2018, [www.ehlers-danlos.com/2017-eds-classification-non-experts/hypermobile-ehlers-danlos-syndrome-clinical-description-natural-history/](http://www.ehlers-danlos.com/2017-eds-classification-non-experts/hypermobile-ehlers-danlos-syndrome-clinical-description-natural-history/).



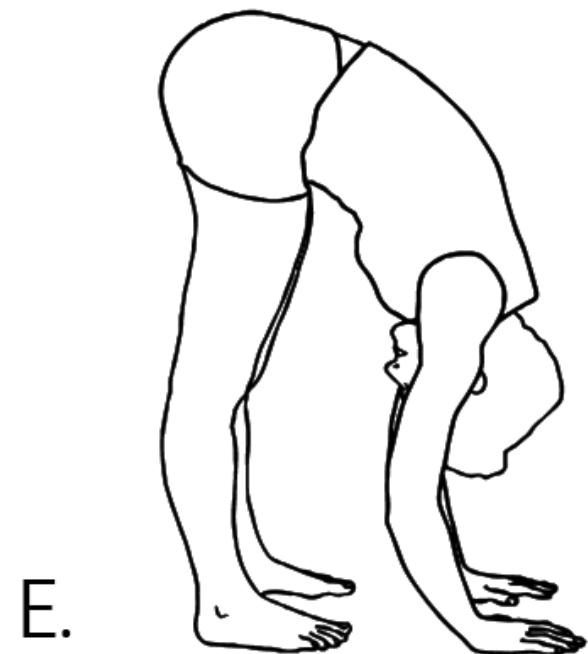
# BEIGHTON SCORE FOR HYPERMOBILITY



"Assessing Joint Hypermobility."  
*The Ehlers Danlos Society*, 10 Oct.  
2019, [www.ehlers-danlos.com/assessing-joint-hypermobility/](http://www.ehlers-danlos.com/assessing-joint-hypermobility/).

## E. SPINE

Can you bend forward and place the palms of your hands flat on the floor in front of your feet without bending your knees? If yes, add one point.





# HYPERMOBILE EHLER'S DANLOS SYNDROME

## CRITERION 1 – Generalized Joint Hypermobility

One of the following selected:

- ☐  $\geq 6$  pre-pubertal children and adolescents
- ☐  $\geq 5$  pubertal men and women to age 50
- ☐  $\geq 4$  men and women over the age of 50

Beighton Score: \_\_\_\_/9



## CRITERION 2 – Two or more of the following features (A, B, or C) must be present

### Feature A (five must be present)

- ☐ Unusually soft or velvety skin
- ☐ Mild skin hyperextensibility
- ☐ Unexplained striae distensae or rubae at the back, groins, thighs, breasts and/or abdomen in adolescents, men or pre-pubertal women without a history of significant gain or loss of body fat or weight
- ☐ Bilateral piezogenic papules of the heel
- ☐ Recurrent or multiple abdominal hernia(s)
- ☐ Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS
- ☐ Pelvic floor, rectal, and/or uterine prolapse in children, men or nulliparous women without a history of morbid obesity or other known predisposing medical condition
- ☐ Dental crowding and high or narrow palate
- ☐ Arachnodactyly, as defined in one or more of the following:
  - (i) positive wrist sign (Walker sign) on both sides, (ii) positive thumb sign (Steinberg sign) on both sides
- ☐ Arm span-to-height ratio  $\geq 1.05$
- ☐ Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria
- ☐ Aortic root dilatation with Z-score  $> +2$

Feature A total: \_\_\_\_/12

### Feature B

- ☐ Positive family history; one or more first-degree relatives independently meeting the current criteria for hEDS

### Feature C (must have at least one)

- ☐ Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months
- ☐ Chronic, widespread pain for  $\geq 3$  months
- ☐ Recurrent joint dislocations or frank joint instability, in the absence of trauma

# Conditions Associated with Hypermobility

The latest research indicates that hypermobility is associated with many conditions, including:

functional gastrointestinal disorders, e.g.  
irritable bowel syndrome, heartburn/GERD  
dysautonomia, including postural orthostatic  
tachycardia syndrome (POTS)  
pelvic and bladder dysfunction  
anxiety disorders and depression  
fatigue and sleep disturbance  
pain & poorer health-related quality of life  
mast cell activation syndrome/disorder (MCAS/MCAD)  
Rheumatic diseases: rheumatoid arthritis, psoriasis and  
psoriatic arthritis, lupus (SLE), and Crohn's disease

- Osteoarthritis
- Headaches (neck instability and pain, muscle spasms in the neck, TMJ dysfunction, medication side effects...)
- Osteoporosis

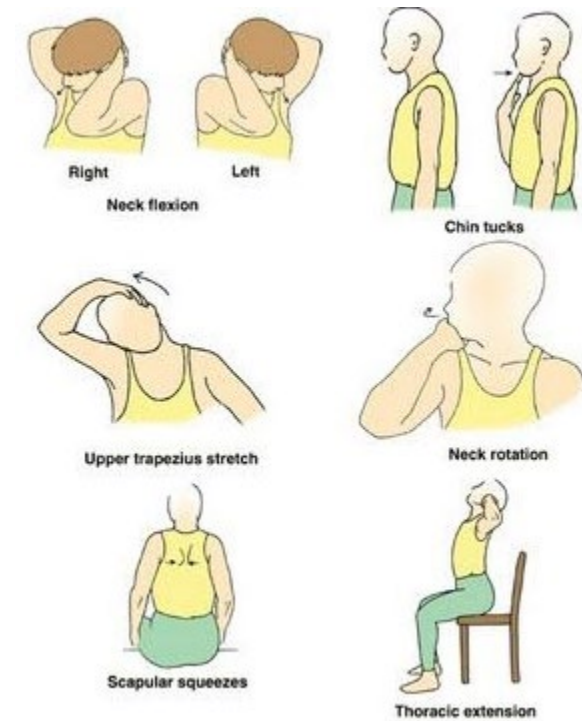
"Hypermobile Ehlers-Danlos Syndrome: Clinical Description and Natural History (for Non-Experts)." *The Ehlers Danlos Society*, 6 Mar. 2018, [www.ehlers-danlos.com/2017-eds-classification-non-experts/hypermobile-ehlers-danlos-syndrome-clinical-description-natural-history/](http://www.ehlers-danlos.com/2017-eds-classification-non-experts/hypermobile-ehlers-danlos-syndrome-clinical-description-natural-history/).

"HEDS Diagnostic Checklist." *The Ehlers Danlos Society*, 19 Sept. 2019, [www.ehlers-danlos.com/heds-diagnostic-checklist/](http://www.ehlers-danlos.com/heds-diagnostic-checklist/).

# OUR PATIENT:

## INCREASING NECK PAIN AND FATIGUE

- Participating in a physical therapy program to help support her joints after her diagnosis of hEDS and was beginning to note some gradual improvements in both pain and joint stability
- 3 weeks ago, was performing neck stretching exercises and felt a “pop”
- Immediate onset of nausea, dizziness, impaired vision, deep sub-occipital neck pain
- No pain associated with the event
- No motor weakness or radiating paresthesias or shooting pains to suggest a radiculopathy
- BUE EMG/NCS performed by PM&R, unremarkable except for mild right-sided CTS
- Symptoms would wax and wane over course of the day, some days worse than others, some times worse than others without clear pattern



- Went to a chiropractor and would feel “almost back to normal” for several hours after a treatment

# CRANIOCERVICAL INSTABILITY AND CRANIOCERVICAL JUNCTION ABNORMALITIES

- Acquired abnormalities of the occipital bone, foramen magnum, or first two cervical vertebrae that decrease the space for the cerebellum, the lower brain stem, cervical spinal cord with associated chronic pathological deformation
- More likely to occur as an acquired “injury” in those with inherited connective tissue diseases
- Estimated prevalence that 1 in 15 people with hEDS will go on to develop craniocervical instability
- May occur as the result of a head or neck injury/trauma (such as whiplash), through repetitive stretching injuries, or even something as simple as rotating one’s head

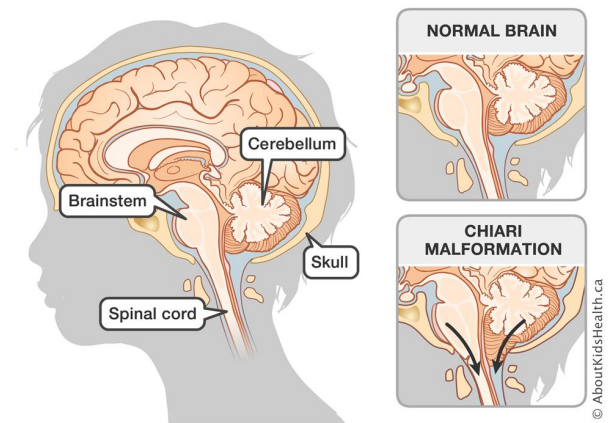
“What Is Craniocervical Instability?” *The Pain Relief Foundation*, [www.thepainrelieffoundation.com/craniocervical-instability/](http://www.thepainrelieffoundation.com/craniocervical-instability/).

Rubin, Michael, et al. “Craniocervical Junction Abnormalities - Neurologic Disorders.” *Merck Manuals Professional Edition*, Merck Manuals, [www.merckmanuals.com/professional/neurologic-disorders/craniocervical-junction-abnormalities/craniocervical-junction-abnormalities](http://www.merckmanuals.com/professional/neurologic-disorders/craniocervical-junction-abnormalities/craniocervical-junction-abnormalities)



# CRANIOCERVICAL INSTABILITY

- **Nerve dysfunction** or even nerve cell death from repetitive stretching or deformative stress of the structures in the involved anatomical area
- **Retroflexion of the odontoid process** as a result of misalignment in the setting of loose ligaments, allowing the odontoid to compress the brainstem
- Thickened **odontoid capsulation** (pannus formation) where the joints are most hypermobile, with the pannus sometimes growing large enough to erode into articular cartilage and bone, allowing the odontoid itself to compress the brainstem
- **Chiari malformation** with downward herniation of the cerebellar tonsils with resulting pressure developing upon both the cerebellum and the brainstem, with possible eventual impedance of CSF flow



“What Is Craniocervical Instability?” *The Pain Relief Foundation*, [www.thepainrelieffoundation.com/craniocervical-instability/](http://www.thepainrelieffoundation.com/craniocervical-instability/).

Rubin, Michael, et al. “Craniocervical Junction Abnormalities - Neurologic Disorders.” *Merck Manuals Professional Edition*, Merck Manuals, [www.merckmanuals.com/professional/neurologic-disorders/craniocervical-junction-abnormalities/craniocervical-junction-abnormalities](http://www.merckmanuals.com/professional/neurologic-disorders/craniocervical-junction-abnormalities/craniocervical-junction-abnormalities)

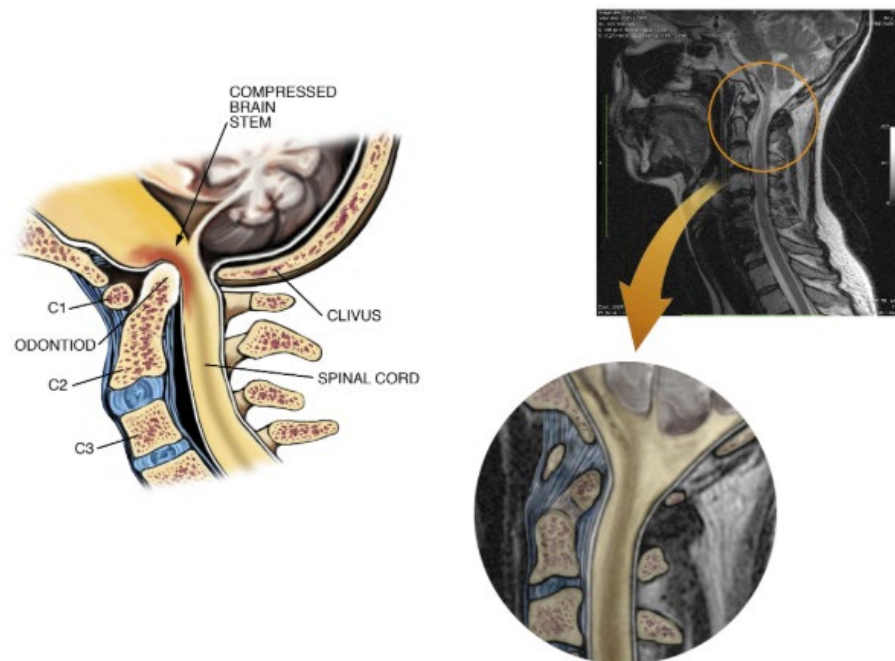
“AboutKidsHealth.” *AboutKidsHealth*, [www.aboutkidshealth.ca/Article?contentid=853&language=English](http://www.aboutkidshealth.ca/Article?contentid=853&language=English).



# CRANIOCERVICAL INSTABILITY

These stretch injuries can result in the following:

- Cranial settling in which the skull settles upon the spine, leading to **basilar invagination** where the odontoid process can project above the foramen magnum at the bottom of the skull

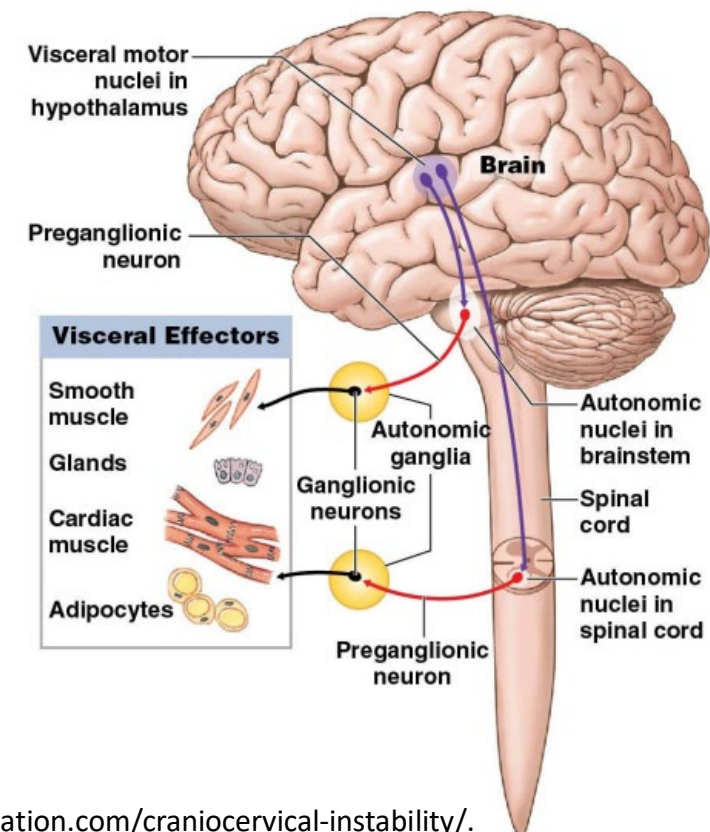


“What Is Craniocervical Instability?” *The Pain Relief Foundation*, [www.thepainrelieffoundation.com/craniocervical-instability/](http://www.thepainrelieffoundation.com/craniocervical-instability/).

Rubin, Michael, et al. “Craniocervical Junction Abnormalities - Neurologic Disorders.” *Merck Manuals Professional Edition*, Merck Manuals, [www.merckmanuals.com/professional/neurologic-disorders/craniocervical-junction-abnormalities/craniocervical-junction-abnormalities](http://www.merckmanuals.com/professional/neurologic-disorders/craniocervical-junction-abnormalities/craniocervical-junction-abnormalities)

# SYMPTOMS OF CCI

- Pressure Headache - impaired CSF flow increases intracranial pressure, which is exacerbated by Valsalva maneuvers including yawning, laughing, crying, coughing, sneezing, or straining
- Heavy Headache - head too heavy for neck support/“bobble-head”
- Dysautonomia – brainstem compression leads to a dysfunctional autonomic nervous system
  - a.) tachycardia
  - b.) heat intolerance
  - c.) orthostatic intolerance
  - d.) syncope
  - e.) delayed gastric emptying
  - f.) excessive and chronic fatigue
  - g.) polydipsia



# SYMPTOMS OF CCI

- Central or Mixed Sleep Apnea
- Neck Pain
- Balance Difficulties
- Facial Pain or Numbness
- Muscle Weakness
- Vertigo or Dizziness
- Tinnitus and Hearing Loss
- Dysphagia
- Reduced Gag Reflex
- Vision Problems
- Nausea & Emesis
- Downward Nystagmus
- Impaired Coordination



# DIAGNOSING CCI

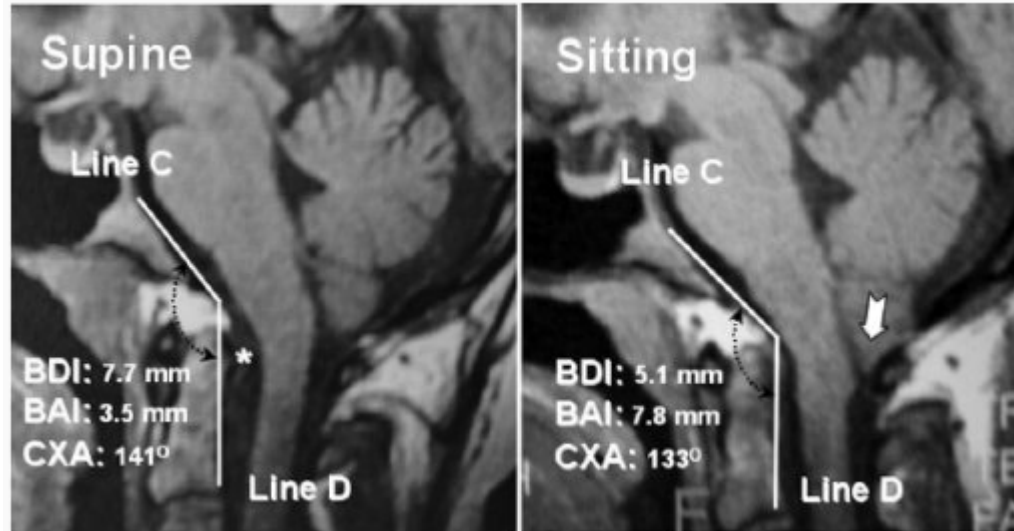
- In the office setting, consider performing **upright** cervical traction (without twisting or rotation) to see if a patient's symptoms improve or resolve
- Alternatively, attempt the “axial load test” in which pressure is applied to the skull in a downward motion and symptoms worsen as a result



- Invasive Cervical Traction (ICT) is an inpatient procedure wherein a patient's head is pulled upward by a pulley system, though this is not widely available
- Gold Standard:
  - Upright MRI **and** Rotational CT scan



# IMAGING IN THE UPRIGHT POSITION



- Supine-lying healthy-appearing MRI of a hEDS individual with CCI showing the cerebellum contained within the skull as would be expected (angle of the odontoid bone is within normal limits)
- On the right, when **upright** MRI is performed, the cerebellar tonsils are downwardly displaced and the odontoid bone is retroflexed, putting pressure upon the brainstem
- In this particular example, this patient's connective tissue was too weak to hold up the cerebellum

"What Is Craniocervical Instability?" *The Pain Relief Foundation*, [www.thepainrelieffoundation.com/craniocervical-instability/](http://www.thepainrelieffoundation.com/craniocervical-instability/).

Rubin, Michael, et al. "Craniocervical Junction Abnormalities - Neurologic Disorders." *Merck Manuals Professional Edition*, Merck Manuals, [www.merckmanuals.com/professional/neurologic-disorders/craniocervical-junction-abnormalities/craniocervical-junction-abnormalities](http://www.merckmanuals.com/professional/neurologic-disorders/craniocervical-junction-abnormalities/craniocervical-junction-abnormalities)



# COMPLETELY OVERWHELMED?



CHRONIC PAIN AND FATIGUE ARE MULTIFACTORIAL,  
CAUSES AND SYMPTOM CAN OVERLAP, AND THE  
LINES OF “OFFICIAL DIAGNOSIS” CAN BE BLURRY...

