

Migraines, Marfan Syndrome & other Connective Tissue Disorders

DIAGNOSTIC AND TREATMENT CONSIDERATIONS

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Roadmap

- What's causing your headaches?
- Focusing on migraines
- Migraine treatment considerations in the setting of Connective Tissue Disorders (CTDs)



Your Questions

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What's causing my headache?

DIAGNOSTIC
CONSIDERATIONS UNIQUE
TO PATIENTS WITH CTDS



What are the different types of headaches?

Specific Diagnostic Considerations among patients with CTDs

- Intracranial Hypotension (“CSF leak”)
- Carotid artery dissection
- Cervicogenic headaches
- Chiari Malformation (CM1)
- Migraines

Intracranial Hypotension

- Leakage of CSF (cerebrospinal fluid)
- Symptoms – most common symptom is headache
 - Headache description –
“Orthostatic Headaches”
(headaches worse with standing and improved upon lying down)



Could you explain headaches related to spinal fluid leaks? How are headaches from spinal fluid leaks caused, what are the symptoms, how is the cause confirmed, and what are the treatment options?

Intracranial Hypotension continued ...

- Risk Factors – CTDs can predispose to dural laxity → tear in the dura → leakage of CSF
- Dural ectasia - a ballooning or outpouching of the dura surrounding the spinal cord, occurs in 63-92% of patients with MFS
- Diagnosis – MRI Brain with contrast can show signs of a leak



What is the incidence of spinal fluid leaks causing headache in the LDS population? Does dural ectasia cause headaches? If so, how can they be treated? What specialists should be seen for this?

Intracranial Hypotension continued ...

- Treatments –
 - Conservative treatment – lying down, caffeine, abdominal binder, hydration
 - Epidural blood patches
 - Fibrin sealant/ “Glue”
 - Surgery
- Post-procedure instructions –
 - Bedrest for hours to days
- Preventive strategies –
 - Avoid straining, bending over, twisting of the trunk etc.

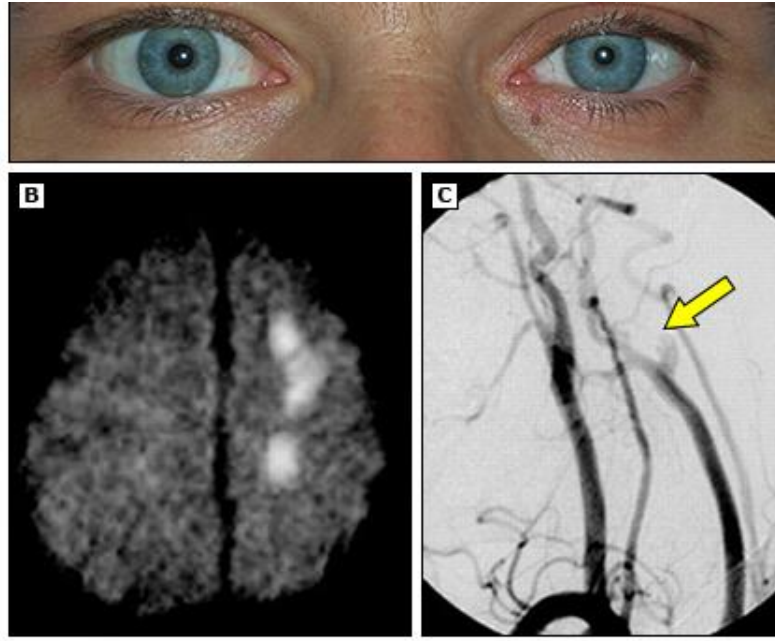


How are CSF leaks treated and can they be prevented?

What are fibrin glue blood patches and are they considered a solution for low-pressure CSF head/neck pain?

Does increased motion cause headaches from dural ectasia? Bumpy car ride or even sex?

Carotid Artery Dissections (CADs)



- A) Horner syndrome
- B) Multiple left frontoparietal acute ischemic lesions on DWI MRI
- C) Carotid angiography with evidence of left extracranial internal carotid artery occlusion

Mazzucco S, Rizzuto N. Teaching Neurolmage: Horner syndrome due to internal carotid artery dissection. *Neurology* 2006; 66:E19. Copyright © 2006 Lippincott Williams & Wilkins.

- Tear in the layers of the arterial wall → blood collect between the layers
- Symptoms – unilateral headache (in 60-95%), face or neck pain (in 25%), Horner's syndrome (in 50%), TIA, stroke
- Risk factors – CTDs impact the integrity of the vessel wall (VEDS, MFS)



Can vein/arterial tortuosity, which is common in LDS, be the source of headaches?
Are headaches related to having aneurysms?

Cervicogenic Headaches

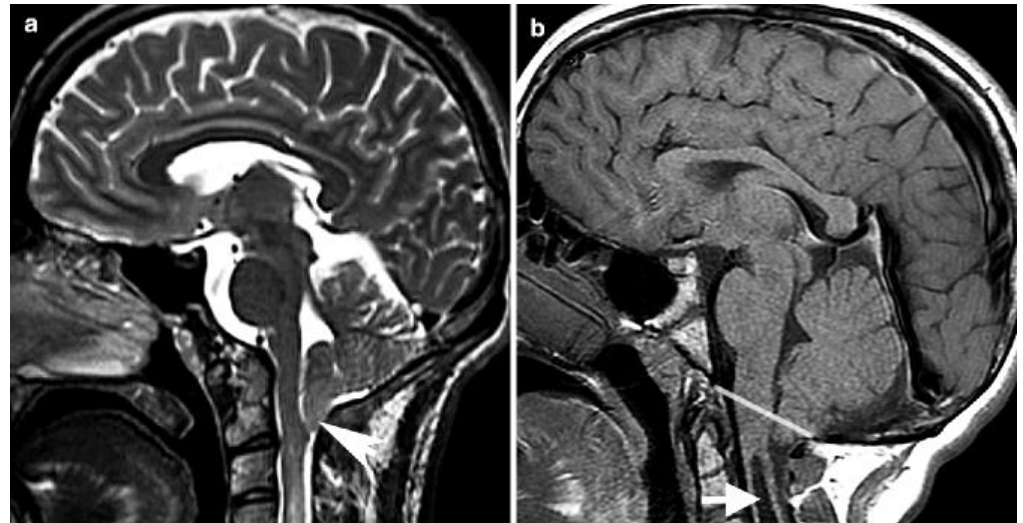
- Disorder of the of the cervical spine causing a headache and oftentimes neck pain
- Headache description – head pain
- Risk factors – cervical hypermobility, joint laxity, scoliosis, atlantoaxial instability (instability between C1 and C2)
- Treatment – physical therapy (assess for atlantoaxial instability first), epidural steroids or facet blocks



Can you please talk about the connection of headaches to problems at the Cranial Cervical Junction: Cranial Cervical Instability, Cerebellar Ectopia/Chiari, Atlanto Axial Instability. What are the symptoms and treatments?

Chiari Malformation (CM1)

- Downward migration of the hindbrain
- Headache description – often occipital or suboccipital, exacerbated by Valsalva maneuvers
- Risk factors – CTDs and EDS have been associated with CM1



- (a) Sagittal T2-weighted MRI of the brain and cervical spine demonstrating findings of Chiari I with cervical ectopia of the cerebellar tonsils with compressed, “pointed” or “peg-like,” morphology (*arrow*)
- (b) More subtle findings of slightly low position of the cerebellar tonsils, 6 mm below a *line* drawn from the basion to the opisthion, with slightly compressed morphology and effacement of CSF at the foramen magnum.

Deans A.E., Barkovich A.J. (2013) Radiology of the Chiari Malformations. In: Tubbs R., Oakes W. (eds) The Chiari Malformations. Springer, New York, NY. https://doi.org/10.1007/978-1-4614-6369-6_12

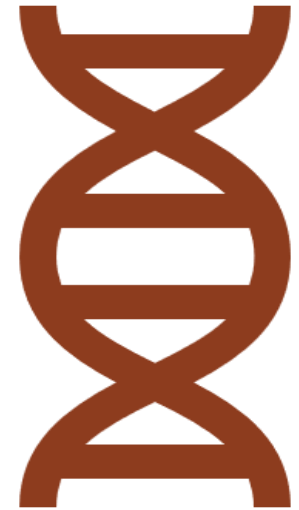
Focusing on Migraines

WHAT IS
MIGRAINE?



What is migraine?

- **Chronic disabling disorder** characterized by attacks of head pain
- State of **altered brain excitability** in genetically susceptible individuals

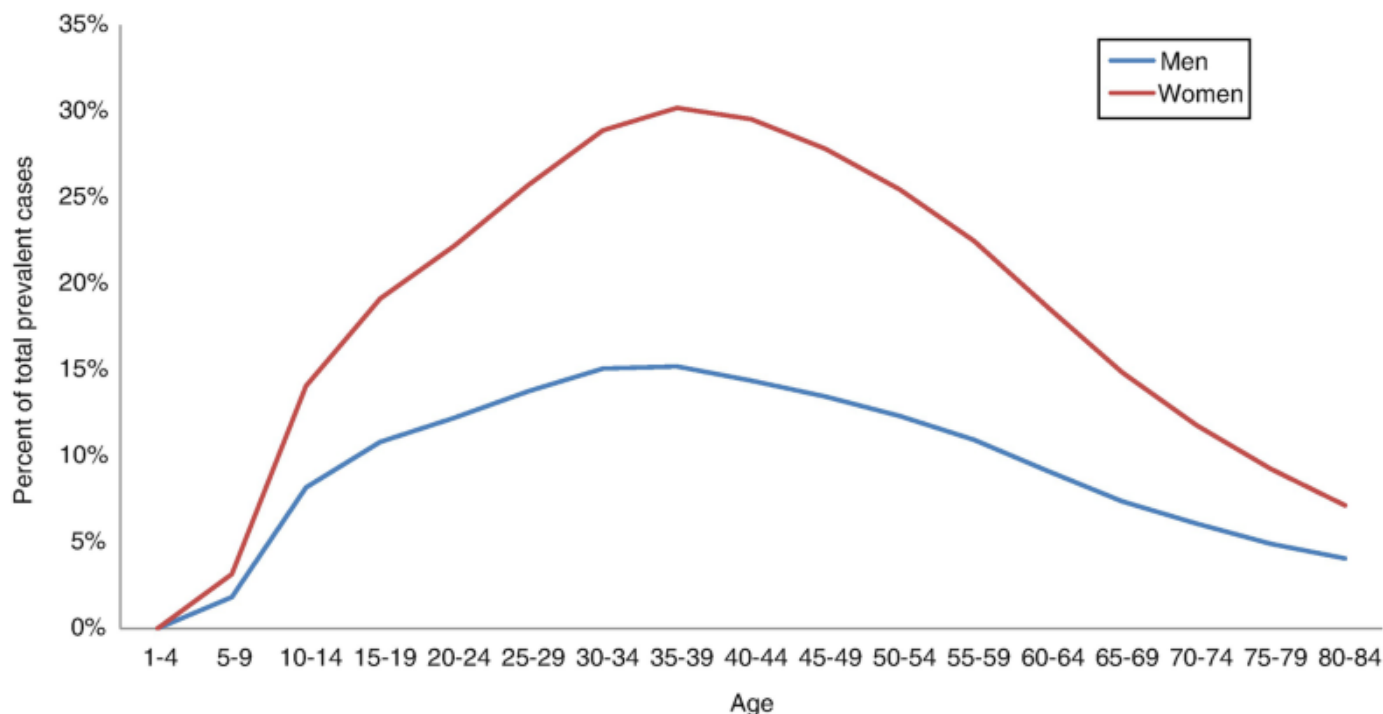


Could Migraines in Marfan patients be a result of head injuries?

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Who gets migraines?

- One billion people worldwide suffer from migraines
- Prevalence of 12% overall (19% in women and 10% in men)
- Migraines **2nd** most disability condition worldwide

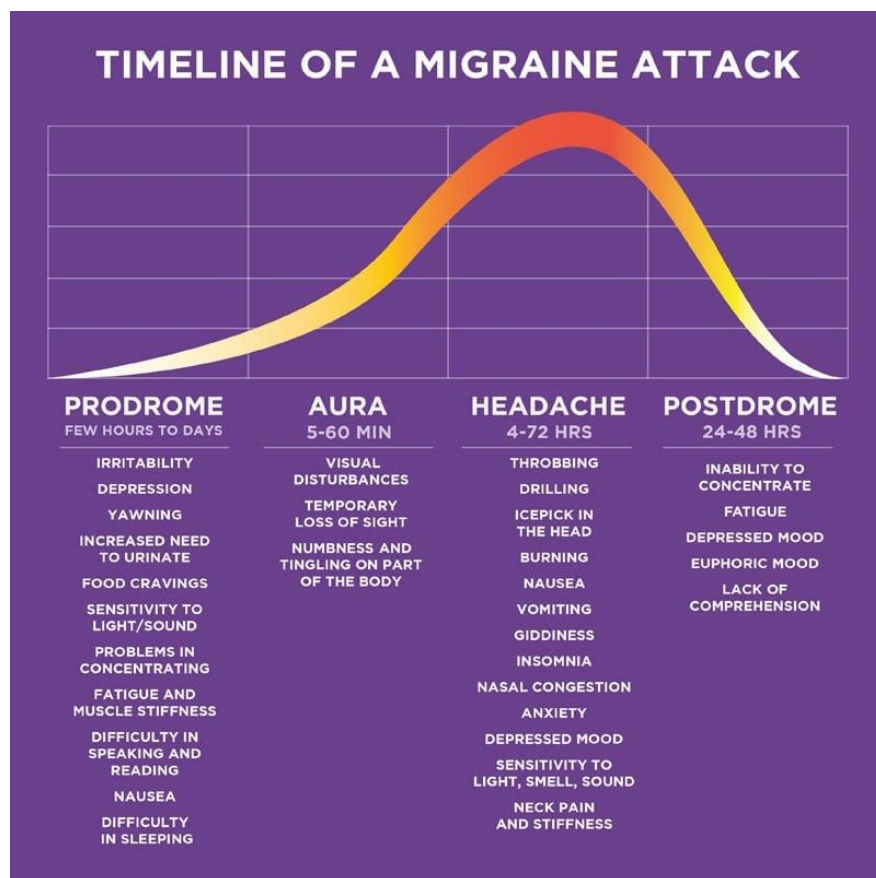


Prevalence of migraine by age and sex. Data from the Global Burden of Disease Study 2016 (GBD 2016)



At what age do migraines begin? Are they more common in women or men?

Phases of migraine



<https://americanmigrainefoundation.org/resource-library/timeline-migraine-attack/>

Migraine without Aura Diagnostic Criteria:

A. At least five attacks¹ fulfilling criteria B-D

B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)^{2;3}

C. Headache has at least two of the following four characteristics:

1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)

D. During headache at least one of the following:

1. nausea and/or vomiting
2. photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis.

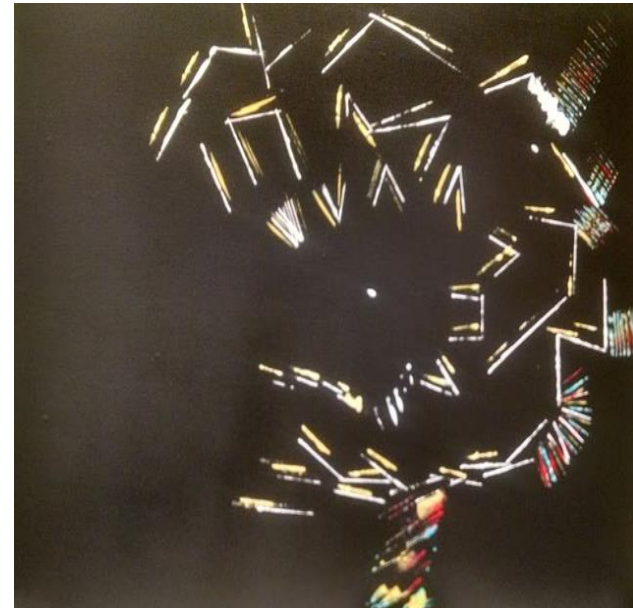


How are migraines diagnosed?/ How can you determine the cause of migraines?

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Migraine with Aura

- 1/3 of migraine attacks are preceded by aura
- Recurrent attacks of reversible neurologic symptoms, developing gradually, usually followed by a headache:
 - Visual
 - Sensory
 - Speech
 - Motor
- 1-3% of patients with a history of migraine have aura without a headache. Tends to occur later in life.



*Is a visual disturbance like a rainbow without a headache a type of migraine?
How common are migraines without direct pain, but with visual symptoms? Any
correlation to headache-less migraines and Marfan/LDS/VEDS?*

Migraine and Stroke

- Migraine with aura is the 3rd most common mimic of strokes
- Migraine with aura is associated with an increased risk of vascular events. However the absolute risk for cardiovascular disease is still quite low

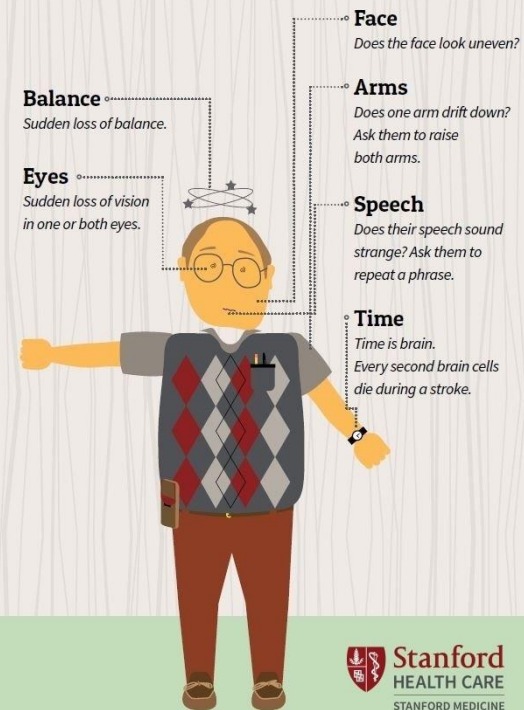
BE FAST

Know the signs of stroke

Stroke is a medical emergency.

For any sign of stroke CALL 911! Every minute counts.

Learn the physical symptoms to swiftly identify stroke and save your life or the lives of loved ones.



<https://stanfordhealthcare.org/stanford-health-care-now/2015/be-fast-infographic.html>



*How do you know if a headache is a stroke or a migraine?
Does migraine increase risk of stroke in LDS patients and how does visual disturbance (aura) relate to this risk?*

Migraine and Connective Tissue Disorders

- Prevalence of Migraine in Marfan Syndrome - Data is limited
 - 3 studies report that the prevalence of migraine is increased in patients with Marfan syndrome
 - Koppen et al. 2012 - **Migraine with aura** is 2.2 times more likely in patients with Marfan syndrome who have undergone aortic root surgery
 - In MFS patients without aortic root replacement but with dilatation not yet requiring operation, no increased prevalence of migraine with aura was found
 - No clear association between migraine with aura and dural ectasias



Are migraines more common in Marfan and Loeys-Dietz than in the general population? If so, why?

What are the causes of migraines in people with Marfan?

What is the connection between Marfan syndrome and migraines?

Are the quality and frequency of migraines in Marfan different from the average migraine patient?

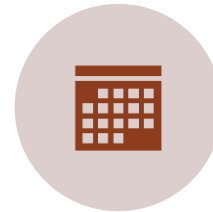
How does Loeys Dietz affect pathophysiology of migraine? Any special tips for prevention and treatment based on connection to Loeys Dietz?

What are the causes of migraines in people with Loeys-Dietz?

Preparing for your appointment



Know your headache – where is the pain, what does it feel like, how long does it last, how often it is it occurring?



Track your headaches with a Calendar, App, or Diary. Keep track of headache activity, potential triggers, response to treatment



Know your **medical history**



Come prepared with **questions**



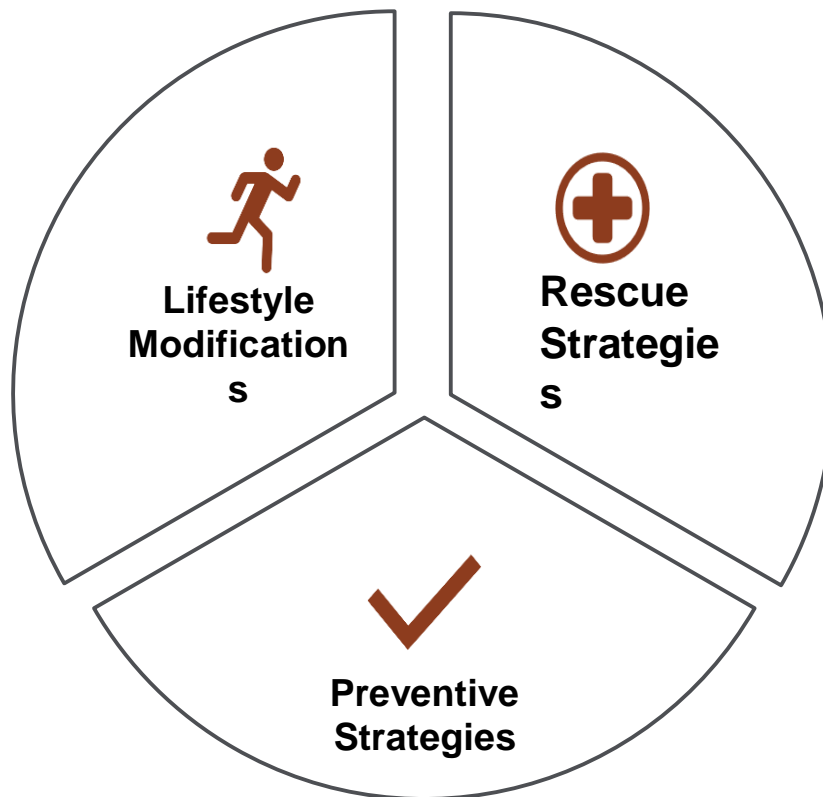
*What type of specialist diagnoses migraines?
Should connective tissue disorder patients regularly follow up with a neurologist the way they do with a cardiologist?*

Migraine treatment considerations for patients with CTDs

NONPHARMACOLOGIC AND
PHARMACOLOGIC
OPTIONS



Elements of a Successful Treatment Strategy

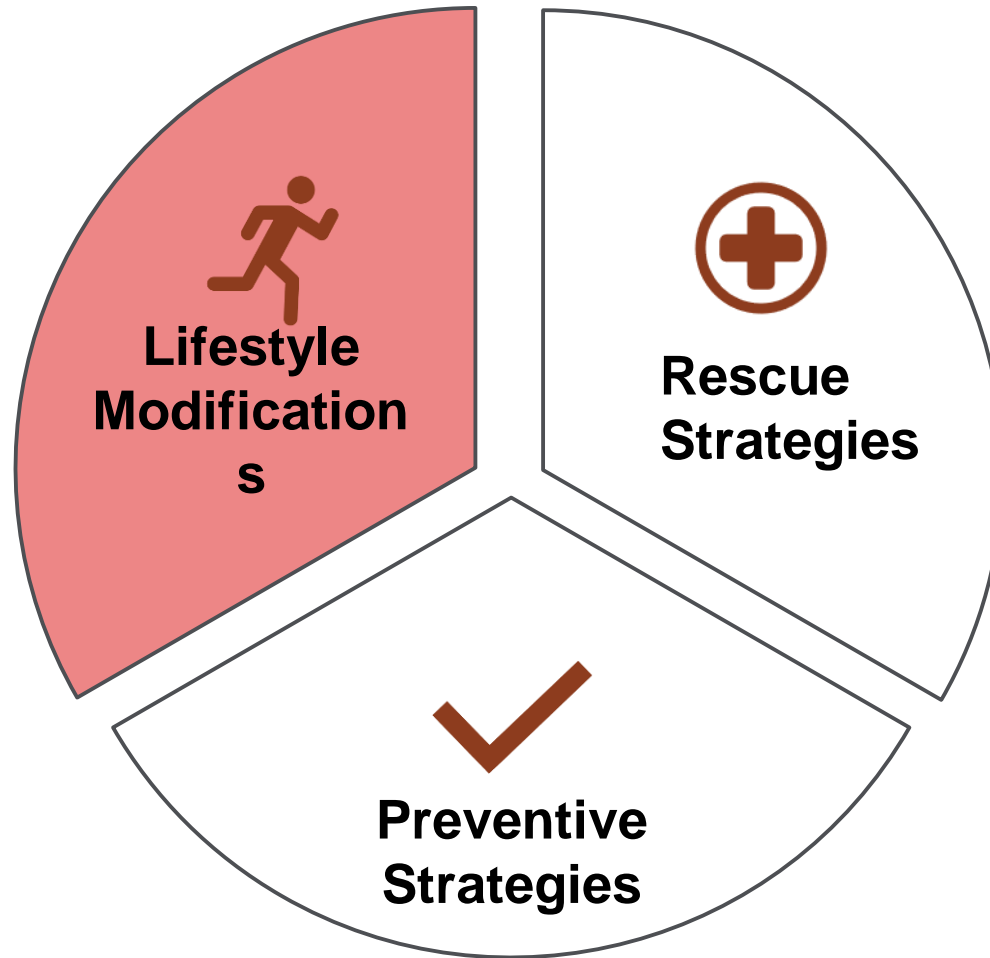


There is no cure for migraines, but they can be successfully managed with nonpharmacologic and pharmacologic tools



Is there any way to get migraines to stop and never come back?

Elements of a Successful Treatment Strategy



Lifestyle Modifications

- Fluctuations to a person's daily schedule can trigger migraines
- Maintaining a regular and stable schedule can help to decrease the likelihood of experiencing migraines



Schedule



Sleep



Eat

There is limited high quality randomized controlled trial data on diet patterns or diet-related triggers to control migraines.



Exercise

***For CTDs - exercise to a moderate level—defined by still being able to carry on a conversation



Is there a correlation between digestive patterns and constant headaches? Would eliminating gluten help?

Potential Migraine Triggers

- Behavioral factors
 - Stress
 - Non-working days
 - Irregular sleep
- Environmental factors
 - Weather - Barometric pressure, heat
 - Odors
- Dietary
 - Alcohol, nitrates, chocolate?
- Physiologic factors
 - Hormonal fluctuations



Why does weather change always cause headaches and migraines in Marfan patients? What can be done to help relieve them?

Why are my migraines much more frequent in certain months of the year?

Can headaches be caused by hormones or diet? Would this be in the connective tissue condition population or for everyone in the general population?

Does when and where you get the migraine make a difference to cause/treatment (e.g., afternoon and evening, rather than morning)?

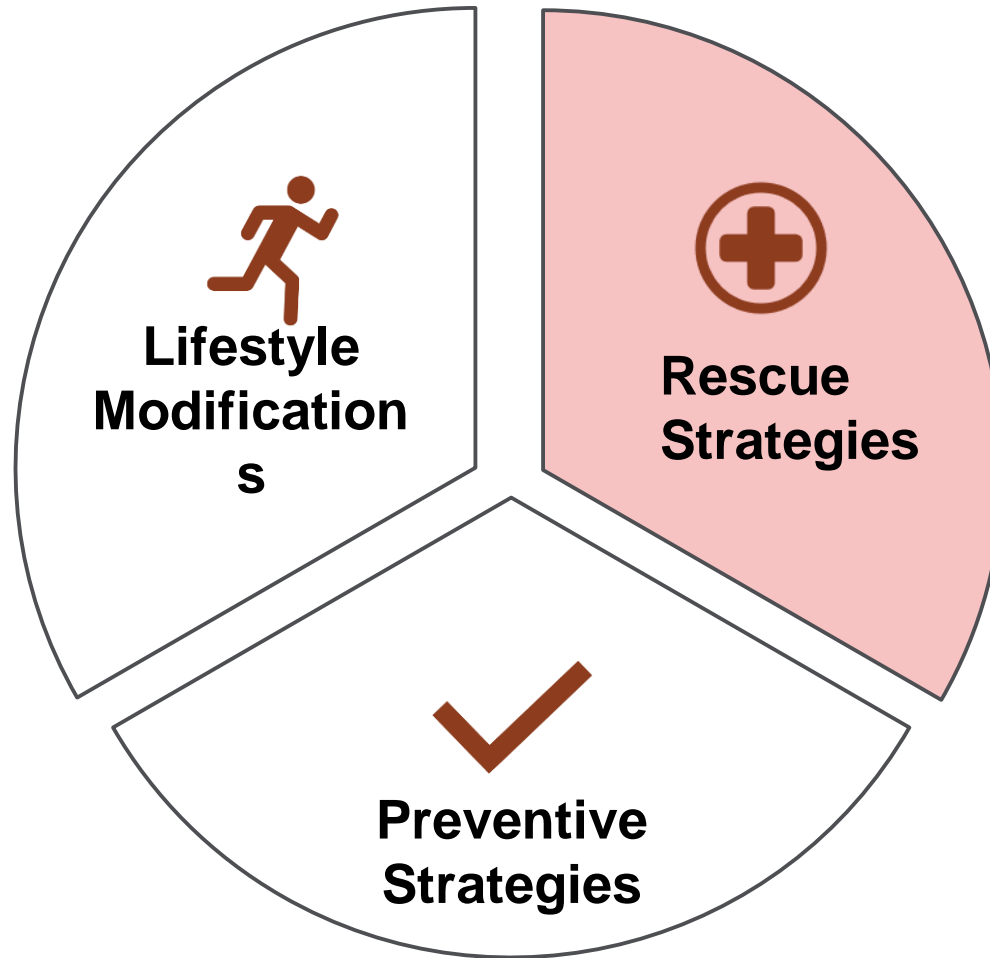
Nonpharmacologic Strategies

- Behavioral Therapies
 - › Relaxation
 - › Biofeedback
 - › Cognitive behavioral therapy
 - › Exercise (aerobic and yoga)
 - › Schedule management
- Physical therapy
- Acupuncture



What are nonmedical treatments for migraines/headaches? Any natural treatments?

Elements of a Successful Treatment Strategy



Pillars of Migraine Rescue Treatment

- **Treat early** in the headache attack
- Use the **correct dose** and formulation
- Treat at least 2 different attacks with the same medication before judging efficacy (unless you experience side effects)
- **Limit use** to no more than 2-3 days per week

Medication Overuse Headaches (MOH)

- Medication overuse headaches (MOH) are headaches that develop as a result of regular overuse of rescue medications





Rescue Strategies

Medications considered safe:

- Acetaminophen
- Anti-emetics – e.g. promethazine, metoclopramide, prochlorperazine (*cause drowsiness, these can cause extrapyramidal side effects, prolong the QT interval*)

Medications to Avoid:

- Triptans (causes vasoconstriction)
- Ergotamine (causes vasoconstriction)
- Butalbital (eg. Fioricet, fiorinal)
- Opiates

Medications that warrant further discussion with your Cardiologist and Neurologist:

- Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) – e.g. diclofenac **naproxen**, ibuprofen, sometimes combined with caffeine
- Muscle relaxants – e.g. baclofen, tizanidine, cyclobenzaprine (*might be avoided due to increased cervical mobility, which may trigger neck pain and/or cervicogenic headaches*)



Are typical migraine medications/therapy safe or contraindicated for people with Marfan, LDS, or VEDS?

Is it safe for someone with Marfan or Loeys-Dietz to take Imitrex?

Are there rescue-meds besides analgesics that are safe for semi-regular use?

Are there ways to decrease their intensity?

Is CBD oil effective/recommended to treat headaches?

Calcitonin gene related peptide (CGRP) – a new therapeutic target to treat migraines

- CGRP is a neuropeptide with a pivotal role in the pathophysiology of migraines
- Multiple newly FDA approved medications block CGRP or its receptor for acute pain relief and as a migraine preventive
- It has receptors throughout the body – nervous system, cardiovascular system, gastrointestinal system
- It is a **potent vasodilator**, and plays a role in regulating vascular resistance and regional organ blood flow
- Animal studies and studies of healthy humans have NOT demonstrated adverse cardiovascular effects of administering CGRP antagonists.

Treatment Class	Drugs	FDA Indication
anti-CGRP mAbs	eptinezumab, fremanezumab, galcanezumab	Migraine prevention
Anti-CGRP receptor mAbs	erenumab	Migraine prevention
Gepants (anti-CGRP receptor antagonists)	ubrogepant, rimegepant	Migraine rescue



Are Emgality injections safe to use in LDS?

Newly FDA approved Rescue Treatment Strategies

Medications to Consider:

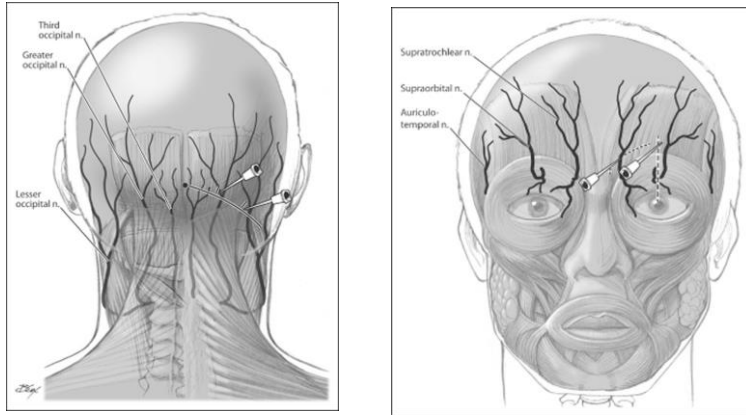
- **Ditans – lasmiditan** (*Side effects can include dizziness, paresthesias, sedation, vertigo, incoordination, cognitive changes, confusion, nausea, vomiting, palpitations, lethargy*)

Medications to Avoid: NA

Medications which deserve additional discussion with your Cardiologist and Neurologist:

- **CGRP Receptor Antagonists** – e.g. rimegepant, ubrogepant (*Side effects can include drowsiness, nausea*)

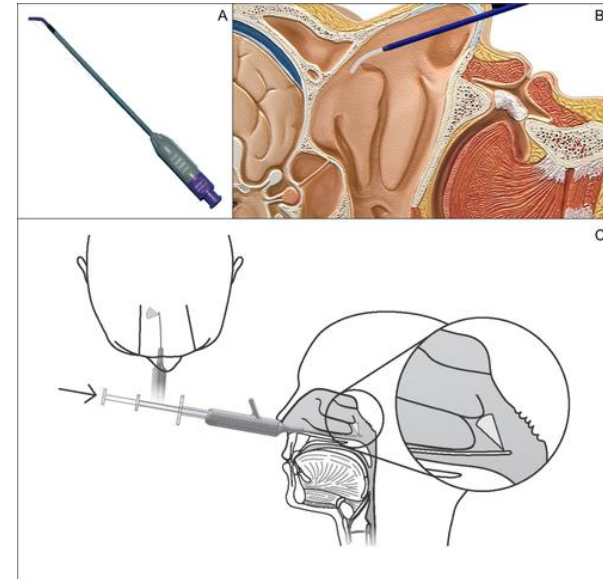
Peripheral Nerve Blocks



Headache: The Journal of Head and Face Pain, Volume: 53, Issue: 3, Pages: 437-446, First published: 13 February 2013, DOI: (10.1111/head.12053)

- Peripheral nerve blocks are injections of anesthetic +/- corticosteroids
- Provide prompt relief with effects that can last longer than the duration of the analgesia
- Generally safe and well-tolerated procedures

Sphenopalatine Ganglion Blocks (SPG)



(A) Sphenocath® nerve block catheter. (B) Allevio® SPG catheter. (C) Tx360® nasal applicator. Images provided courtesy of Dolor Technologies, LLC, Jet Medical, and Tian Medical.

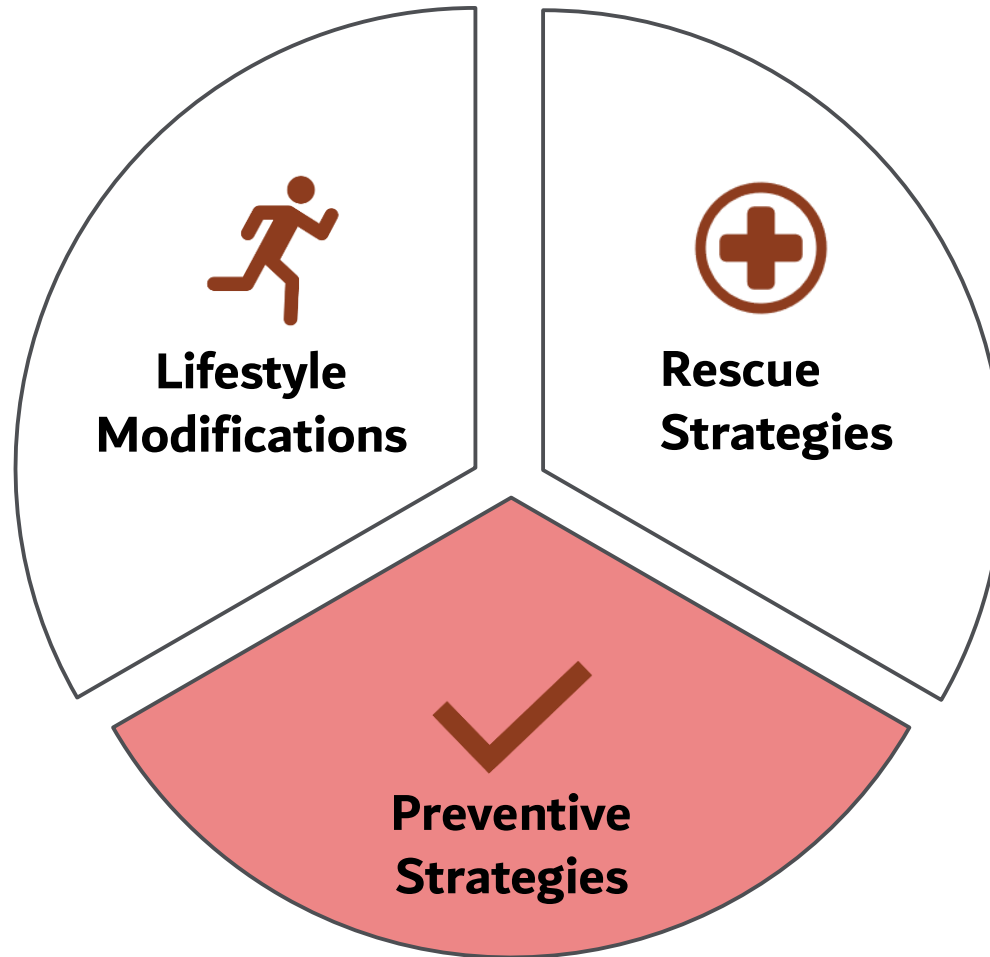
Headache: The Journal of Head and Face Pain, Volume: 56, Issue: 2, Pages: 240-258, First published: 30 November 2015, DOI: (10.1111/head.12729)

- SPG blocks – limited literature on efficacy
- Seems to be well-tolerated and safe



What is an SPG block (sphenoganglion block or sphenocath) and how safe is it for someone with Marfan? Are there any unique risks?

Elements of a Successful Treatment Strategy



Pillars of Migraine Preventive Treatments

GOALS

- To **reduce the frequency, severity and duration of your pain**
- Improve responsiveness to acute treatments
- **Improve function** and reduce disability
- Reduce reliance on acute treatments
- Enhance a sense of **personal control**
- Improve health related quality of life
- Reduce headache-related distress and psychological symptoms

GUIDELINES

- Attacks **interfere with daily routines** despite acute treatment
- **Frequent attacks** (> 4 monthly headache days)
- Contraindication to, failure or overuse of acute medications
- **Adverse events** with acute treatments
- Your preference



Preventive Pharmacologic Treatment Strategies

Medications to Consider:

- **Nutraceuticals** – e.g. riboflavin (B2), magnesium, Coenzyme Q10
- **Anti-seizure drugs** – e.g. Valproate, topiramate
- **Anti-depressants** – e.g. Tricyclic antidepressants, venlafaxine.
- **Simvastatin + Vitamin D**

Medications to Avoid: NA

Medications which deserve additional discussion with your Cardiologist and Neurologist:

- **Anti-hypertensives** – e.g. beta blockers, calcium channel blockers, angiotensin receptor blockers. (Be cautious with orthostatic hypotension and low blood pressure when using anti-hypertensives.)
- **Onabotulinum toxinA** – *consider avoiding injections in the cervical paraspinals* in patients with increased cervical mobility, which may trigger neck pain and/or cervicogenic headaches
- **CGRP Monoclonal Antibody Receptor/Molecule Antagonists** – e.g. eptinezumab, fremanezumab, galcanezumab, erenumab



What classes of drugs are currently recommended for treatment or prevention of migraine for people with Marfan?

Are anti-depressants a good option for treating migraines/headaches?

Are Emgality injections safe to use in LDS?

What is the best treatment for chronic migraine?



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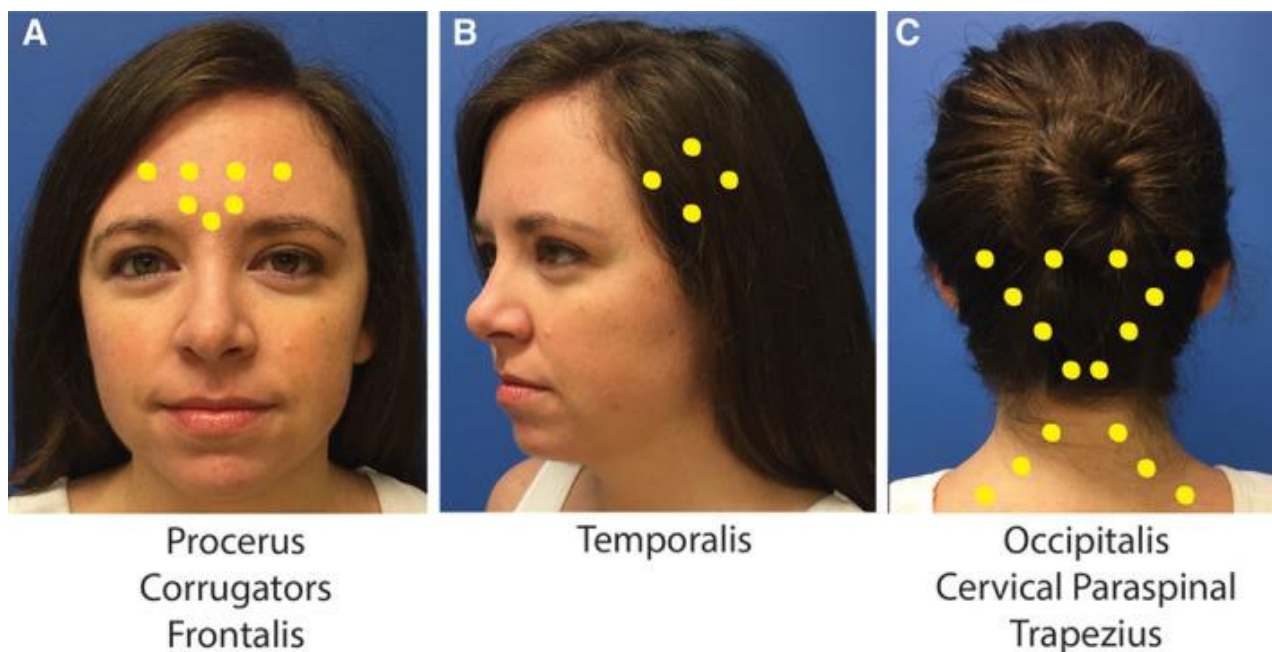
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Onabotulinum toxinA

- 31 injections done according to the PREEMPT protocol every 12 weeks
- FDA approved for chronic migraine prevention
- Peak benefit may require multiple treatments



Plast Reconstr Surg Glob Open. 2017 Mar; 5(3): e1270.

Published online 2017 Mar 28. doi: 10.1097/GOX.0000000000001270



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Treatment with Devices

Remote electrical neuromodulation device (*Nerivio*) –

Wireless battery-operated device, worn on the upper arm, controlled by a smartphone, for acute treatment of migraines



<https://theranica.com/homepage/>

Supra-orbital external trigeminal nerve stimulation (*Cefaly*) –

worn on the forehead, for acute and preventive treatment



<https://americanmigrainefoundation.org/resource-library/understanding-migrainecefaly-for-migraine-prevention/>

Cervical non-invasive Vagus Nerve Stimulation Device (*GammaCore*) – for acute treatment, data for efficacy as a preventive treatment is not robust



www.gammacore.com

Key Take Aways



There are many causes of headaches and some unique diagnostic considerations for patients with Connective Tissue Disorders



Migraines occur with increased frequency among patients with Connective Tissue Disorders



Treatment should involve a Multidisciplinary approach with lifestyle modifications, rescue, and preventive strategies



Speak with your Cardiologist and Headache specialist or Neurologist about risks and benefits of specific migraine treatments.

THANK YOU

QUESTIONS?

