

Management of complex pain in children and adults with EDS and CRPS

Pradeep Chopra, MD
Assistant Professor (Clinical)
Brown Medical School.
USA

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Introduction

- Pain Medicine specialist with a special interest in complex pains in adults and children
- Training and Fellowship, Harvard Medical school in Pain Medicine
- Assistant Professor (Clinical) – Brown Medical School, Rhode Island, USA

Disclosure and disclaimer

- I have no actual or potential conflict of interest in relation to this presentation or program
- This presentation will discuss “off-label” uses of medications
- Discussions in this presentation are for a general information purposes only. Please discuss with your physician your own particular treatment. This presentation or discussion is NOT meant to take the place of your doctor.

Ehlers Danlos Syndromes

- Two important things to remember:
 1. Weak connective tissue
 2. Poor joint position sense (proprioception)

Ehlers Danlos Syndromes

- The human body is connected together.
- Bones are connected at joints with ligaments, muscles to bones.
- The tissue that connects them is called 'connective tissue'
- Connective tissue – 'connects' everything in our body – joints, skin, ligaments, intestines, muscles.....

- In Ehlers Danlos Syndromes – the connective tissue is weak, it stretches easily and breaks
- Once it breaks it does not heal well.

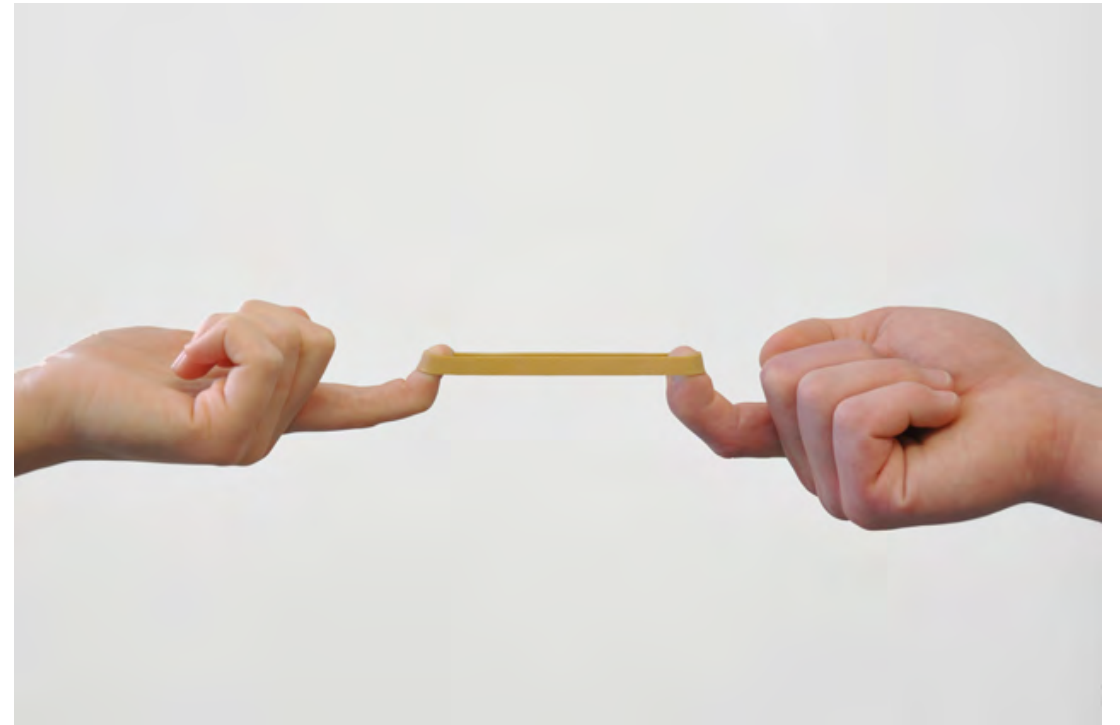
Connective tissue – non –Ehlers Danlos Syndromes

- Connective tissue is made of collagen
- The connective tissue is strong
- Does not stretch as much
- Does not break easily
- Heals well when broken



Connective tissue – Ehlers Danlos Syndromes

- Connective tissue is made of collagen
- The connective tissue is weak
- It stretches easily
- It breaks easily
- It does not heal well



Weak scar in EDS



Joint Position sense

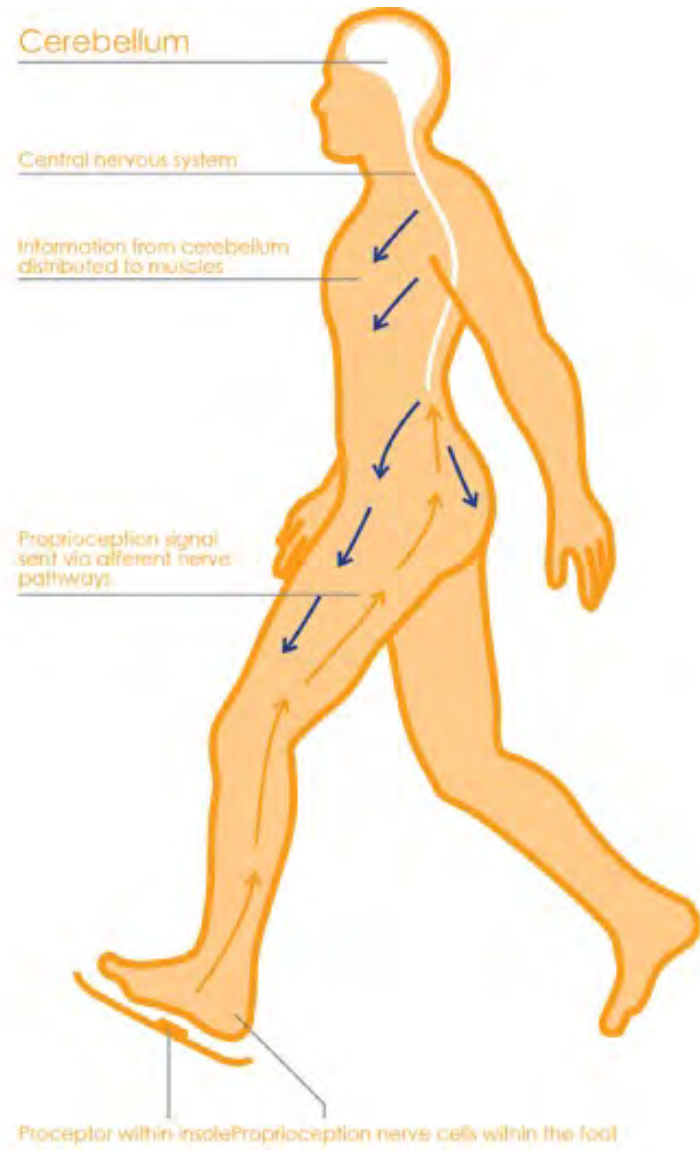
Proprioception

The body's ability to sense movement of the joints
and their position

Proprioception – Joint sense

- The brain constantly gets information from the joints as to the exact position of the limbs in space.
- It helps us walk, use our arms, maintain our posture without tipping over.
- Protects our joints from over extending and our muscles from over stretching
- EDS – poor proprioception. That is what makes them uncoordinated

Proprioception – Joint sense



Proprioception – Joint position sense

- With repetitive injury, wear and tear of joints, we start to lose proprioception
- This is seen with almost any condition that affects joints EDS, arthritis, athletics
- Patients tend to lose their balance easily
- When they lose balance, the body tends to counteract by straining other muscles.

Proprioception – Joint position sense

- With poor Joint Position sense (Proprioception) we do not use our muscles efficiently.
- This causes fatigue, tiredness and pain

Toddler with poor proprioception



Compression clothes

- The brain uses signals from the skin to understand the position of the joints and muscles.
- Wearing compression clothes helps the brain understand the position of the body parts, muscles

Compression garments



Proprioception exercises

- Juggling
- Balance board or wobble board
- Stork standing (stand on one leg)
- Stand up paddle board (SUP)
- Sitting on exercise ball
- Exercise in water – walking, treading but NO swimming

Proprioception exercises



Wobble board



Stand up paddle board



Exercise in water - walking

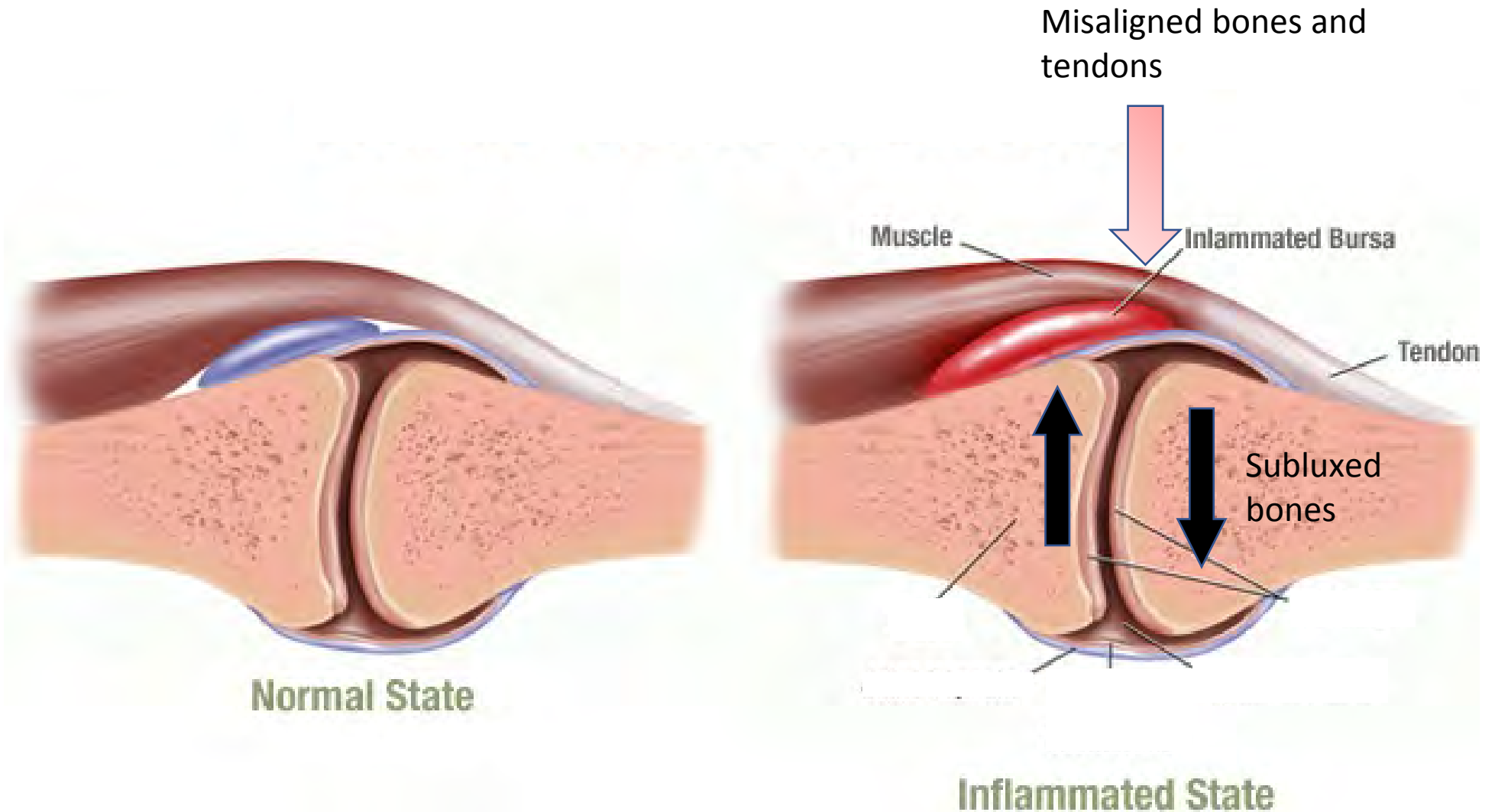


Aquatic therapy

- Best form of exercise in EDS
- The contact of water with the skin helps the brain move your muscles more efficiently
- The water makes us weigh less which takes the load off the joints allowing us to exercise freely
- Avoid swimming – it strains the joints of the neck and shoulders.

Tendonitis and bursitis

Tendonitis and bursitis in EDS



Tendonitis and bursitis in EDS

- Treatment lies in correcting the underlying problem –
 - correct bracing to align the joints
 - Correct posture (especially standing)
 - Avoid repetitive use of joint
 - Maintain proper balance

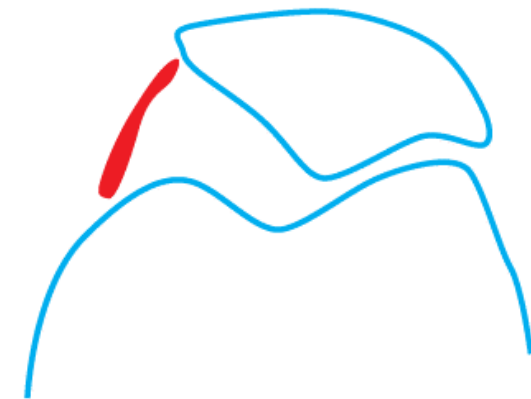
Subluxations and Dislocations

Pain in subluxation and Dislocations

- When a joint subluxes or dislocates, the pain is usually from muscle spasms around the joint.
- Pain from capsular stretch
- Not as much from the bones



Dislocation



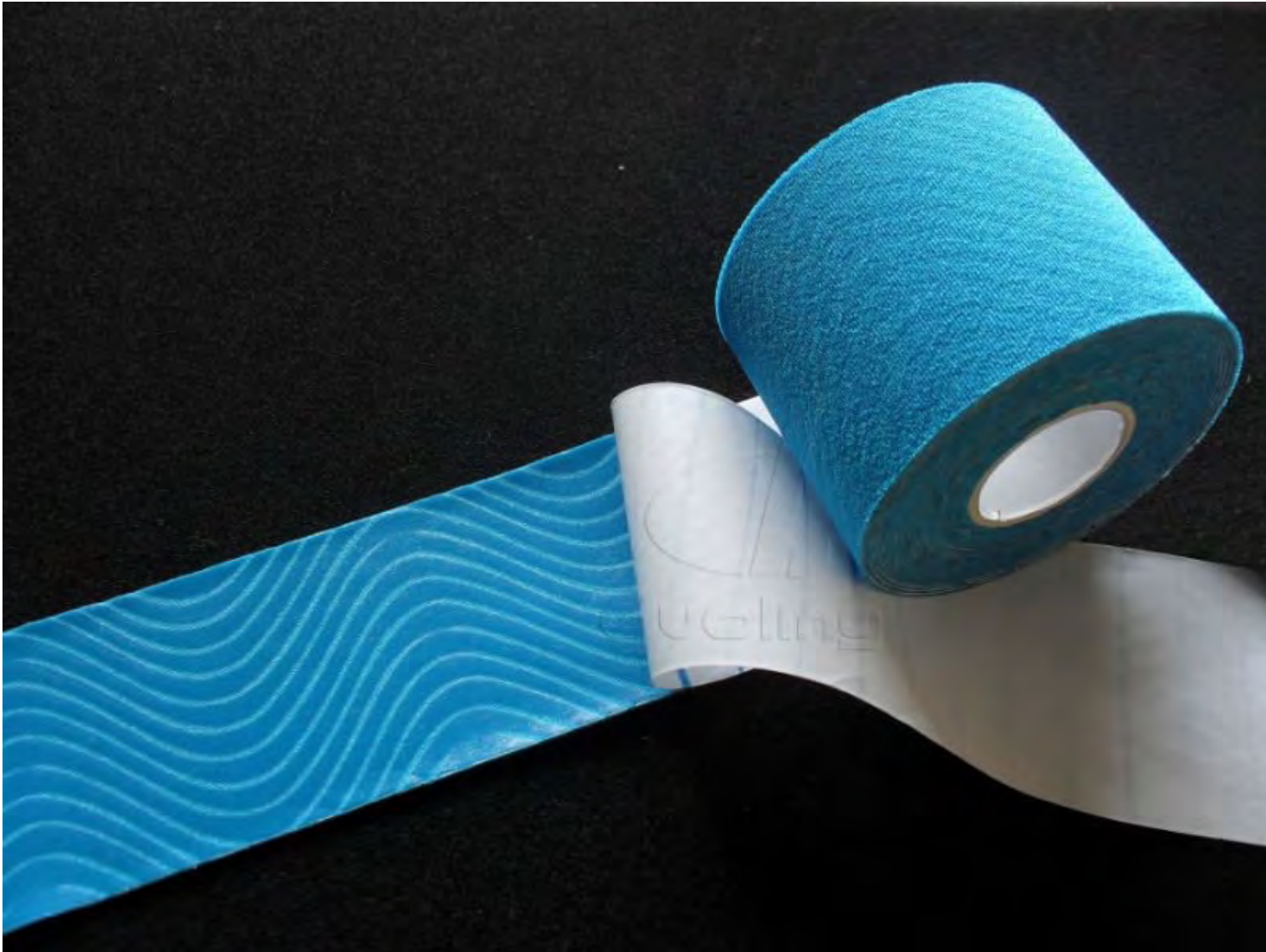
Subluxation

Neuromuscular taping (Kinesio™)

Kinesio™ taping - mechanism

- Mimics the superficial layer of skin – after 10 minutes you can not feel it
- Designed to stretch
- Porous – allows for drying easily. You can take a shower with it on
- The adhesive is applied in a wave like pattern to mimic the qualities of fingerprints.

Finger print pattern



Kinesio™ taping - mechanism

- The tape stimulates the sensors in the skin as we move – improves proprioception
- Helps reduce swelling

Kinesio™ taping - uses

- Reduces pain
- Improves Proprioception
- Relaxes muscles
- Stabilizes joints
- Supports weak joints
- Reduces swelling

Kinesio taping helpful for

- Neck
- Upper back
- Lower back – SI joints, muscles
- Wrist
- Shoulders
- Knees
- Ankles and feet

Kinesio taping – EDS knee

- A combination of two strips of 25 cm in length and 2.5cm in width along the collateral ligament (sides of the knee) using 50% tape tension applied distally (furthest) to proximal, a horizontal tape below the patella 25 cm in length and 2.5 cm in width applied with 25% tension and lastly a Y tape 30 cm in length and 5cm in width cut with 5cm in initial base applied laterally to the patella with no tape tension.

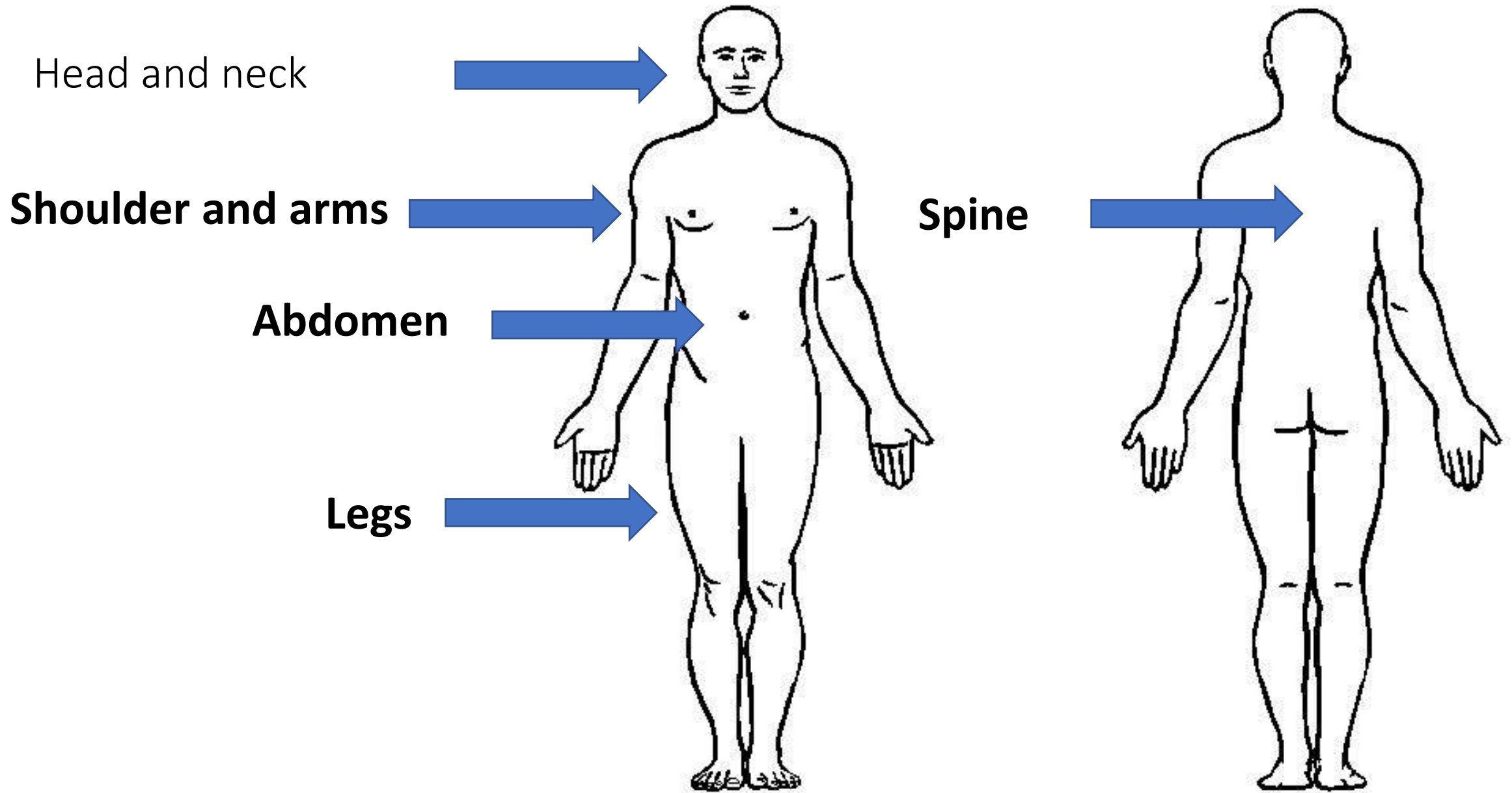


Ther Adv Musculoskelet Dis. 2015 Feb; 7(1): 3–10. doi: 10.1177/1759720X14564561 PMID: PMC4314299 The effects of neuromuscular taping on gait walking strategy in a patient with joint hypermobility syndrome/Ehlers–Danlos syndrome hypermobility type Filippo Camerota, Manuela Galli, Veronica Cimolin, corresponding author Claudia Celletti, Andrea Ancillao, David Blow, and Giorgio Albertini Author information

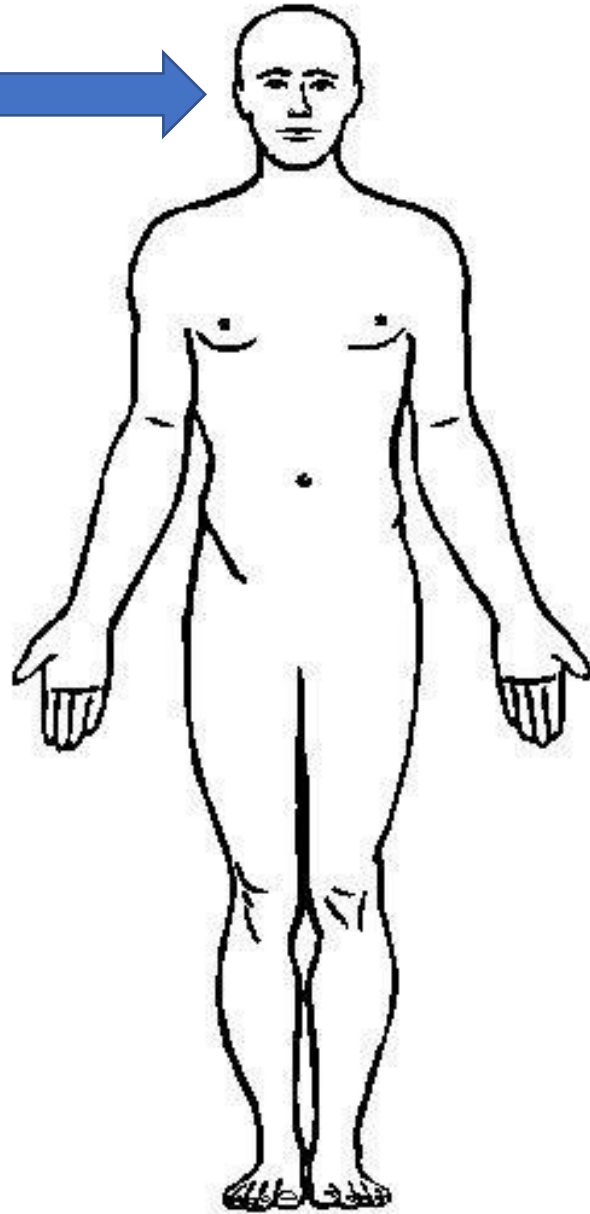
Ehlers-Danlos syndromes (EDS)

- Ehlers-Danlos syndromes are a variation in body type.
- It is another form of the human body.
- EDS itself can't be treated.
- But symptoms in EDS arise from secondary conditions which can be treated.
- Hypermobile people have different medical conditions from non-hypermobile people.

Pain in EDS by body regions



Head and neck



Common causes of headaches

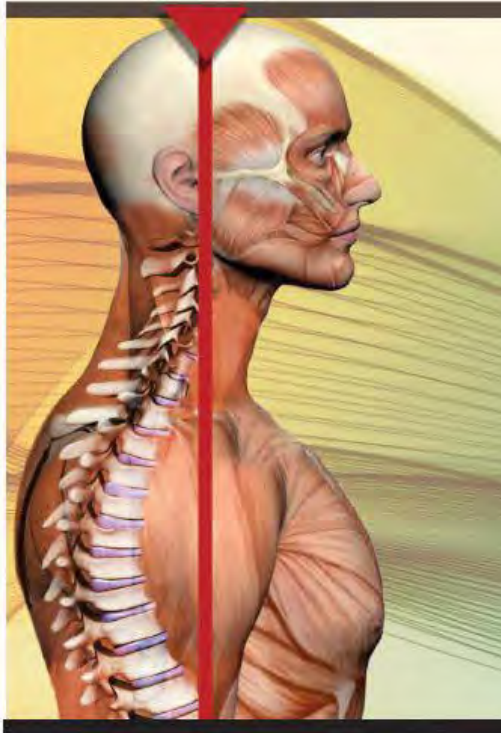
1. Chiari malformation
2. Cervicogenic Headaches – from muscles
3. Temporo Mandibular joint dysfunction (Craniofacial pain)
4. Vision – blurry
5. POTS / Dysautonomia
6. Tethered Cord syndrome (TCF)
7. Spontaneous CSF (Cerebrospinal) leak
8. Cranio Cervical Instability (Instability of the neck and head)

Neck pain and headaches

- A common cause of neck pain is posture
- Chin poking forward position
- Correction is easy.
- Before looking at other reasons, correct this first
- If there are other reasons like cervical instability, Chiari malformation etc – these need to be addressed

Wie schwer ist dein Kopf?

5.4Kg / 12 lbs.



NORMAL POSTURE

Wie schwer ist dein Kopf?

5.4Kg / 12 lbs.

14.5Kg / 32 lbs.



NORMAL POSTURE

2 INCHES FORWARD

5 cm forward

Wie schwer ist dein Kopf?

5.4Kg / 12 lbs.

14.5 Kg / 32 lbs.

19 Kg / 42 lbs.



NORMAL POSTURE

2 INCHES FORWARD

3 INCHES FORWARD

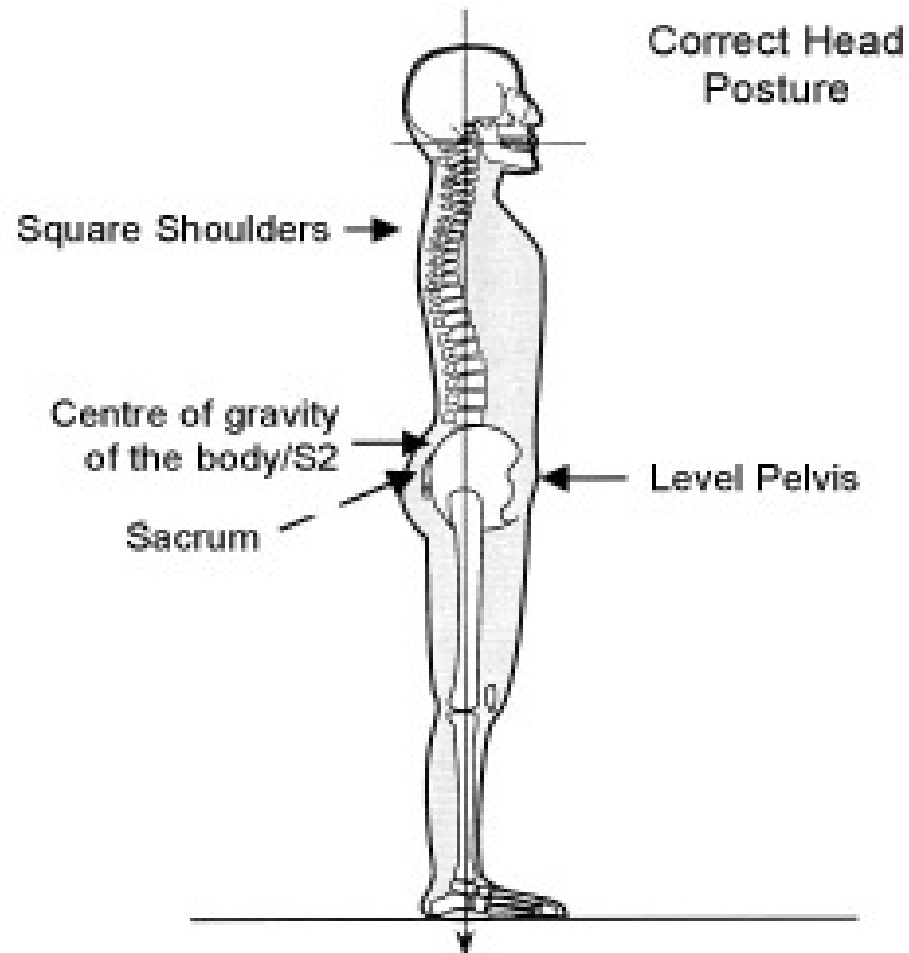
5 cm forward

7.6 cm forward

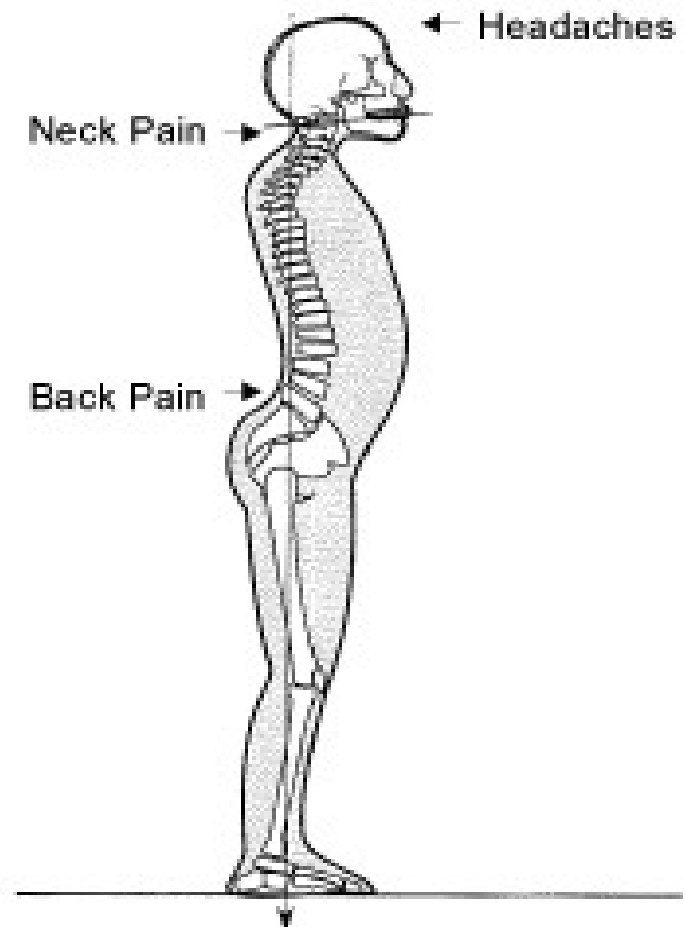


Pain from a poor posture

Good Posture



Poor Posture



Common reasons for poor posture in EDS

- Vision – Blurry vision. Usually intermittent
- Postural Orthostatic Intolerance (POTS)
- Laxity of spinal ligaments
- Instability of the head on the neck (Cranio Cervical instability)

Managing neck pain and headaches from poor posture

- Place index finger in front of chin and push back head gently till ears are in line with shoulders
- Large monitor
- Post it note on monitor to remind you
- Vision correction
- Manage POTS

Lift the phone, don't drop your head!



Upper back pain in women with EDS

- Sports bra with:
- racer back (cross straps).
- Wide straps.
- Front closure
- Proper fitting – recommend getting it done professionally.
- May have to consider reduction mammoplasty (Breast reduction) in severe intractable upper back pain



High Racer back – Posture bra



Compression garments to improve proprioception



Cervical spine (Neck) issues in EDS

- Cranio Cervical Instability
- C1-C2 instability
- Lower Cervical kyphosis
- Cervical disc degeneration (commonly at C4-C5 and C5-C6)
- Chiari malformation

Cranio Cervical instability in EDS

- The neck is stabilized by ligaments
- Laxity of the ligaments causes the joints in the neck to move more
- Excessive movement of the joints in the neck causes cranio cervical instability

Cranio Cervical instability (CCI) – Upper cervical (neck) – C0 to C2

- Neck pain / stiffness
- Headaches
- Dizziness
- Paresthesia to face
- Fatigue
- Poor sleep
- Tinnitus (ringing in ears)
- Nausea
- Poor vision
- Anxiety
- Lightheaded
- Poor balance
- Difficulty swallowing

Cranio Cervical instability (CCI) – Lower cervical (neck) – C3 to C7

- Muscle spasms
- Crepitation (cracking sensation)
- Neck pain
- Tingling and numbness in fingers

Imaging for Cranio Cervical Instability

- Need functional imaging technology
- Static pictures are not helpful
- Functional computerized tomography (fCT scan)
 - Flexion.
 - Rotate neck left 90 degrees.
 - Rotate neck right 90 degrees.
- Functional MRI (fMRI)
- Digital motion x-ray (DMX)

Cranio Cervical instability in EDS – CT scan findings

1. Displacement
2. Wide interpedicle distance
3. Wide interspinal (interlaminar) distance
4. Widening of facet joints
5. Disruption of posterior vertebral body line

Cranio Cervical Instability - management

- Mild to moderate:
 - Neck muscles strengthening exercises
 - Hard cervical collar (Vista Aspen collar)
 - Prolotherapy – Hackett-Hemwell prolotherapy
- Severe Instability:
 - Surgical fusion



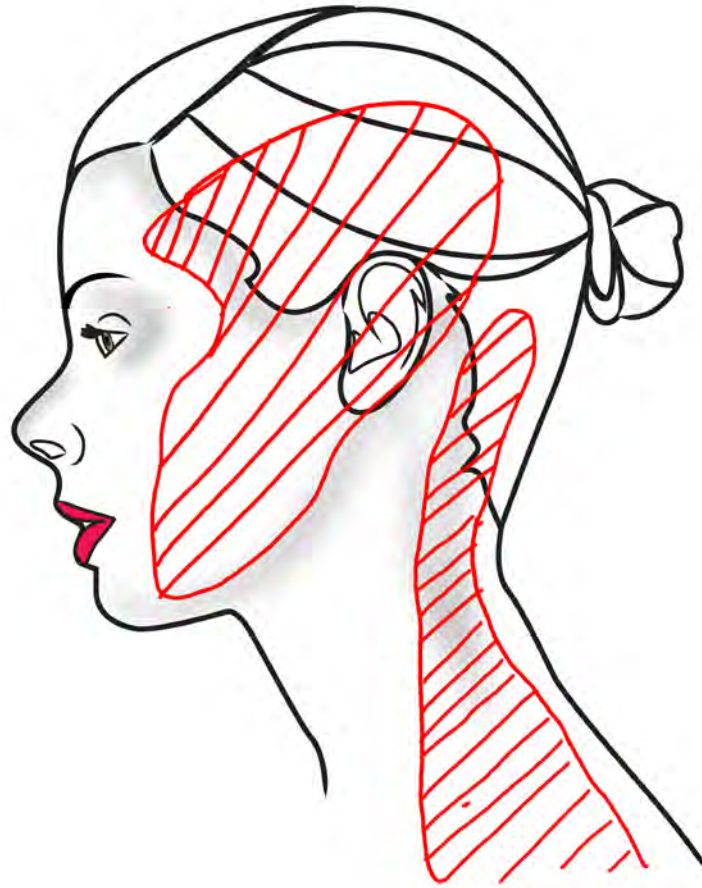
TMJ Pain

Temporo Mandibular Joint Dysfunction



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Temporo-Mandibular joint pain



TMJ Pain

- Very closely related to neck issues
- Clicking noises
- Clenching, grinding
- Pain with chewing
- Difficulty opening mouth wide (eating an apple)
- Jaw locking up

Temporo-mandibular joint dysfunction (TMJ)

- Present in 70%
- Treatment: avoid excessive mouth opening, caution when yawning,
- orthodontist specializing in TMJ
- Avoid over the counter mouth guards

Dental issues in Ehlers Danlos Syndromes

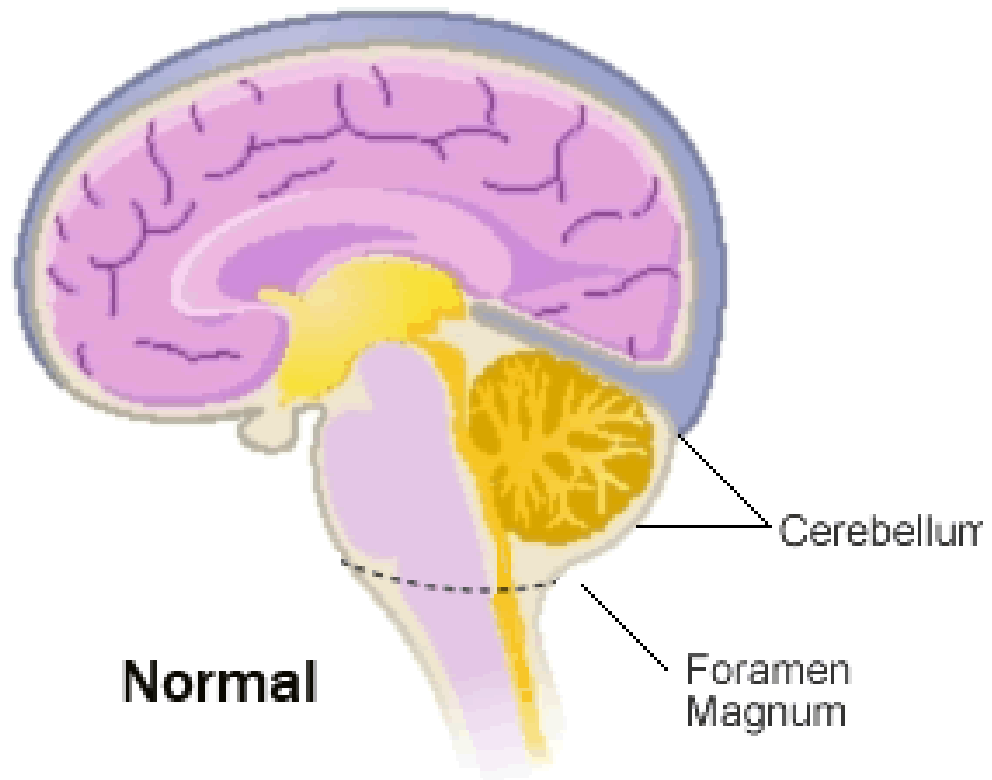
- Teeth: weak and thin enamel, prone to cavities
- Gums: periodontal gum weakness, gingivitis, easy bleeding, delayed healing after surgery, tissue breakdown after surgery (tooth extraction), gum recession and pocketing
- Poor tooth stability, crowding of teeth
- Local anesthetic may not work or onset will be delayed

Chiari Malformation

Symptoms of Chiari Malformation

- Neck pain
- Balance problems
- Numbness or paresthesia's to arms or legs
- Dizziness
- Difficulty swallowing
- Poor Hand co-ordination
- Ringing or buzzing in the ears
- Hearing loss
- Nausea, vomiting
- Headaches made worse by coughing or straining
- Fine motor skills
- Muscle weakness
- Vision problems

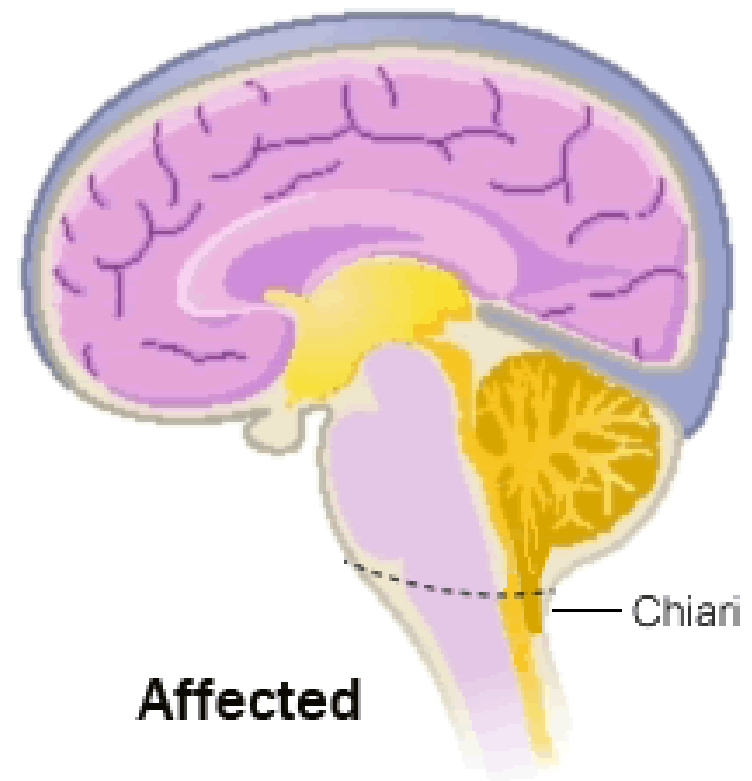
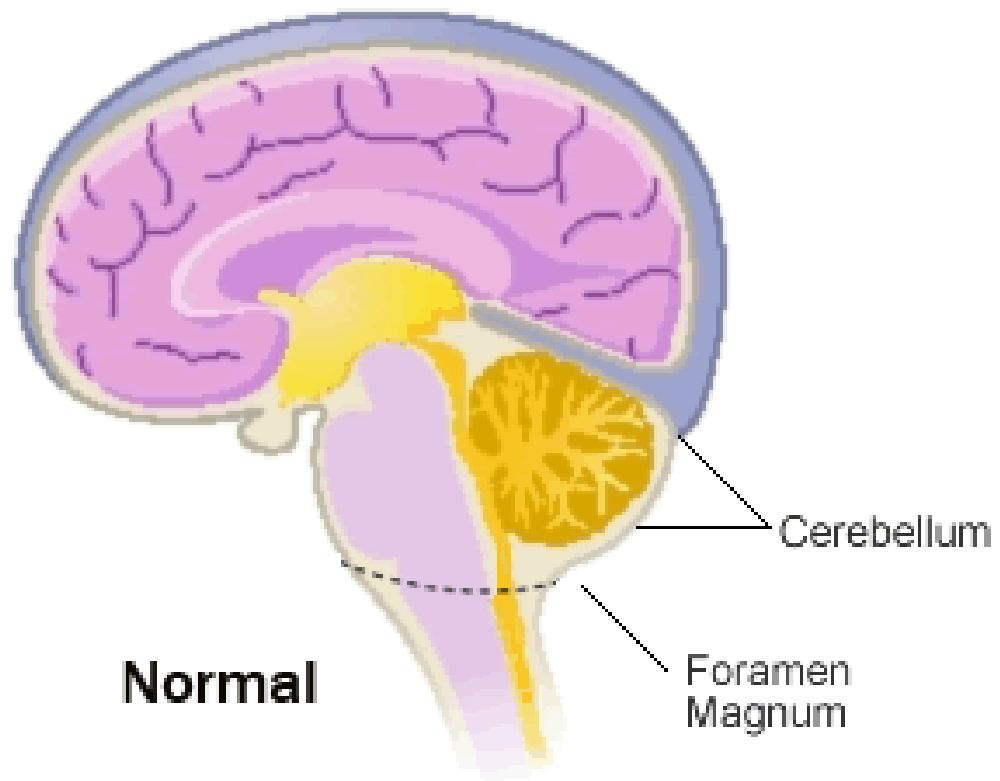
Chiari malformation



<http://www.craniofacial.vcu.edu/conditions/chiari.html>

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Chiari malformation



<http://www.craniofacial.vcu.edu/conditions/chiari.html>

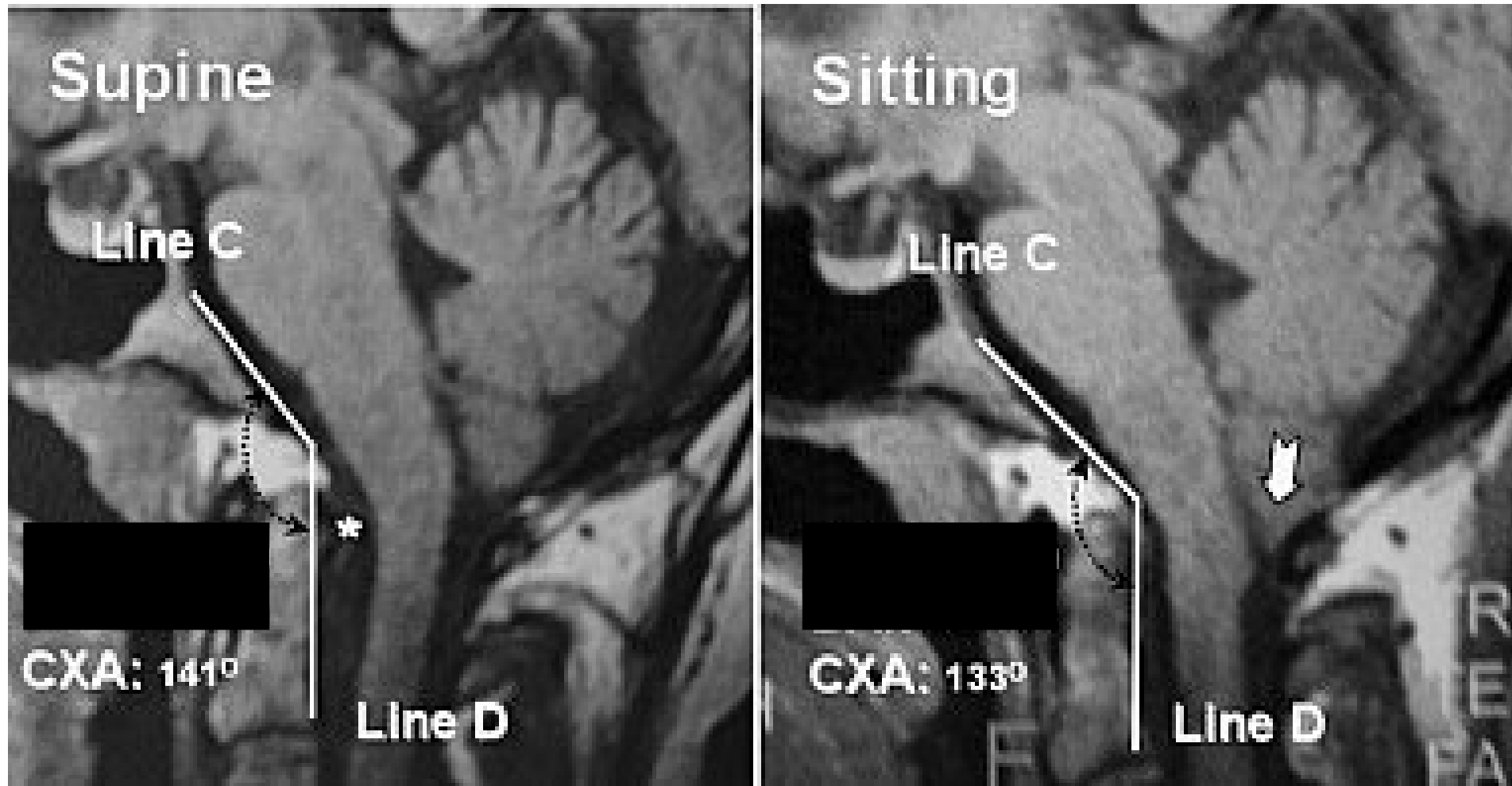
Chiari Malformation and EDS

- Higher incidence of Chiari in EDS
- Cranial settling (loose ligaments)
- Posterior gliding of condyles
- Reduction of the clivus-axis angles, clivus atlas angle, atlas-axis angle.
- Upright MRI is far more valuable in EDS

Thomas H. Milhorat, M.D.,¹ Paolo A. Bolognese, M.D.,¹ Misao Nishikawa, M.D.,¹ Nazli B. McDonnell, M.D., Ph.D.,² And Clair A. Francomano, M.D.³ Syndrome of occipitoatlantoaxial hypermobility, cranial settling, and Chiari malformation Type I in patients with hereditary disorders of connective tissue. J Neurosurg Spine 7:601–609, 2007

Cranial Settling in EDS- Deformative stresses on the brain stem, lower cranial nerves, spinal cord

Clivo-axial angle normal 140°



MRI for Chiari Malformation in EDS

- MRI in upright position – Important
- Ask for measurement of the clivus-axis angles, Grabb-Oakes angle
- An upright MRI is also very important for rotational, flexion-extension films.
- Patients with EDS have cranial settling when they are in the upright position

Pain in the back

Spinal Instability

- The spine is made up of multiple joints – held together by ligaments and muscles.
- Spinal instability with reflex muscle spasms may happen at any level

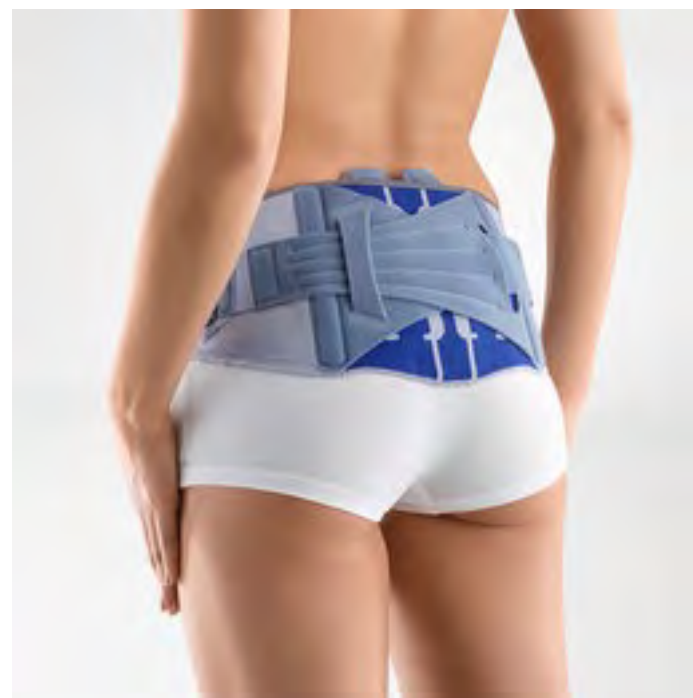
Spinal Instability

- Thoracic spine – subluxations where the ribs meet the spine (costo—vertebral joints)
- Lumbar spine – subluxations of the facet joints.
- Sacroiliac joint pain (SI Joint) – maybe more from uneven posture or pain from joints in the legs

Spinal pain

- If the pain is from the joints in the spine – postural correction, compression garments, muscle strengthening
- Steroid injections not very helpful but can be used in very select cases

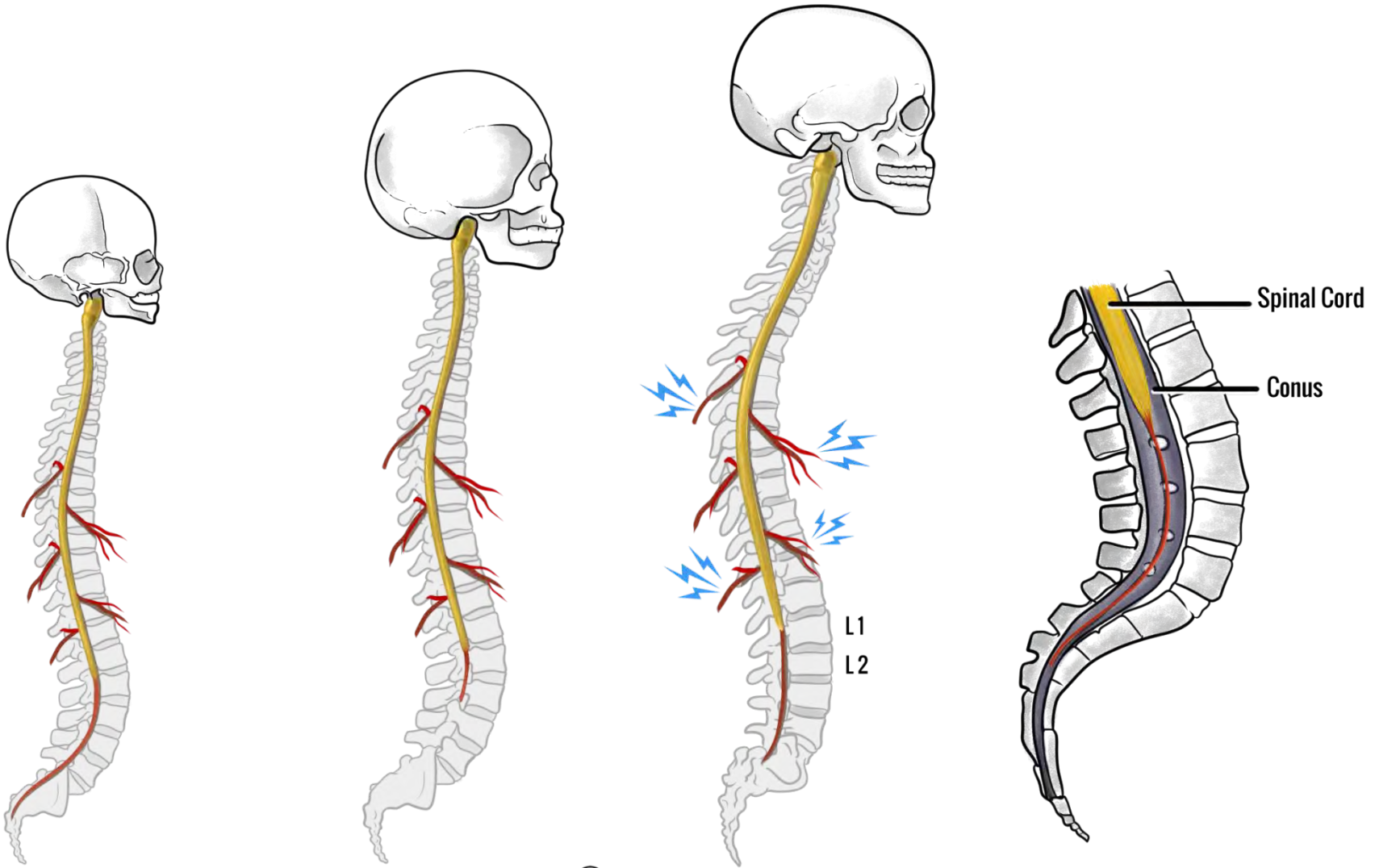
Brace for lumbar and Sacroiliac joint



Tethered Cord Syndrome

Tethered Cord Syndrome (TCS)

- The spinal cord hangs freely in the spine, it slides up and down in a sheath (much like a sword in a sheath)
- In TCS the lower end is tethered to the bottom of the spine
- As we grow taller, the spinal cord gets stretched.



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Tethered cord syndrome

- Back pain and leg pains and complaints: “aches” and “burns” not sharp
- Teenager: Pain, Asymmetrical cramps in legs, pigeon toed, knock knees
- Young adults: Pain, Spasticity and increased reflexes, weakness in legs
- Constipation - severe
- Foot and leg deformities, flat feet
- Scoliosis
- Tingling and numbness in pelvis and feet

Tethered cord syndrome and Complex Regional Pain Syndrome (CRPS)

- One of the presentations of tethered cord syndrome is severe pain in the legs and presents with the same symptoms as CRPS

Neurogenic bladder

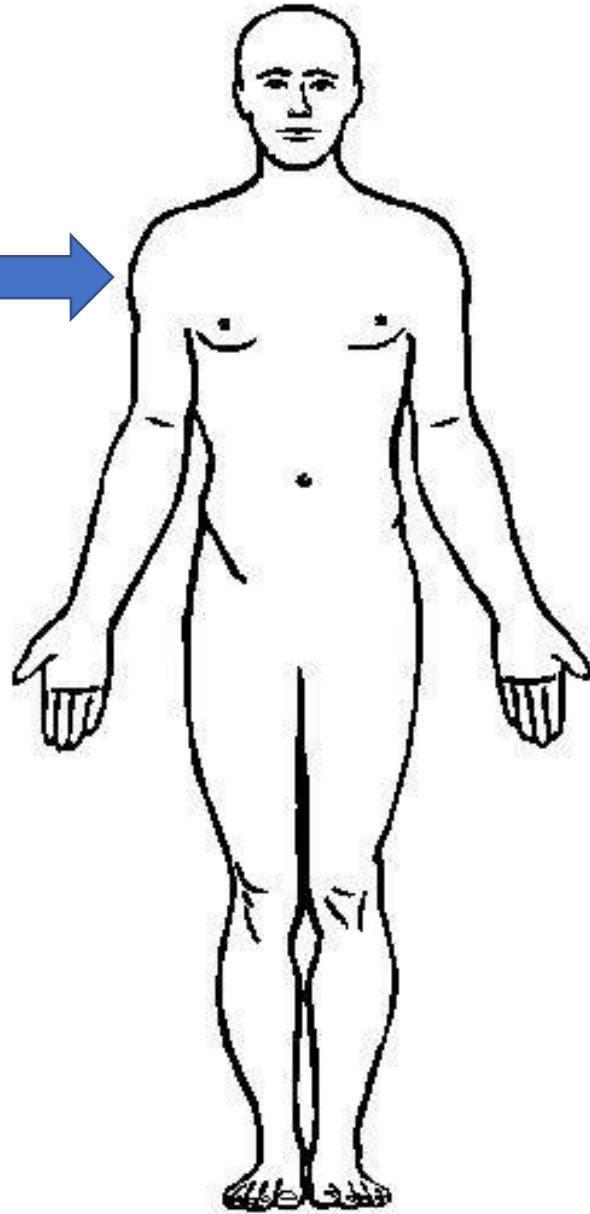
- Increased frequency
- Urgency
- Sense of incomplete evacuation of bladder
- Incontinence to urine
- More than 3 urinary tract infections in a year

Tethered Cord Syndrome and EDS

- MRI is NOT a useful tool for diagnosing TCS
- Diagnosis is based on clinical history and examination
- A urodynamic study maybe helpful

Pain in the arms in EDS

Shoulder and arms



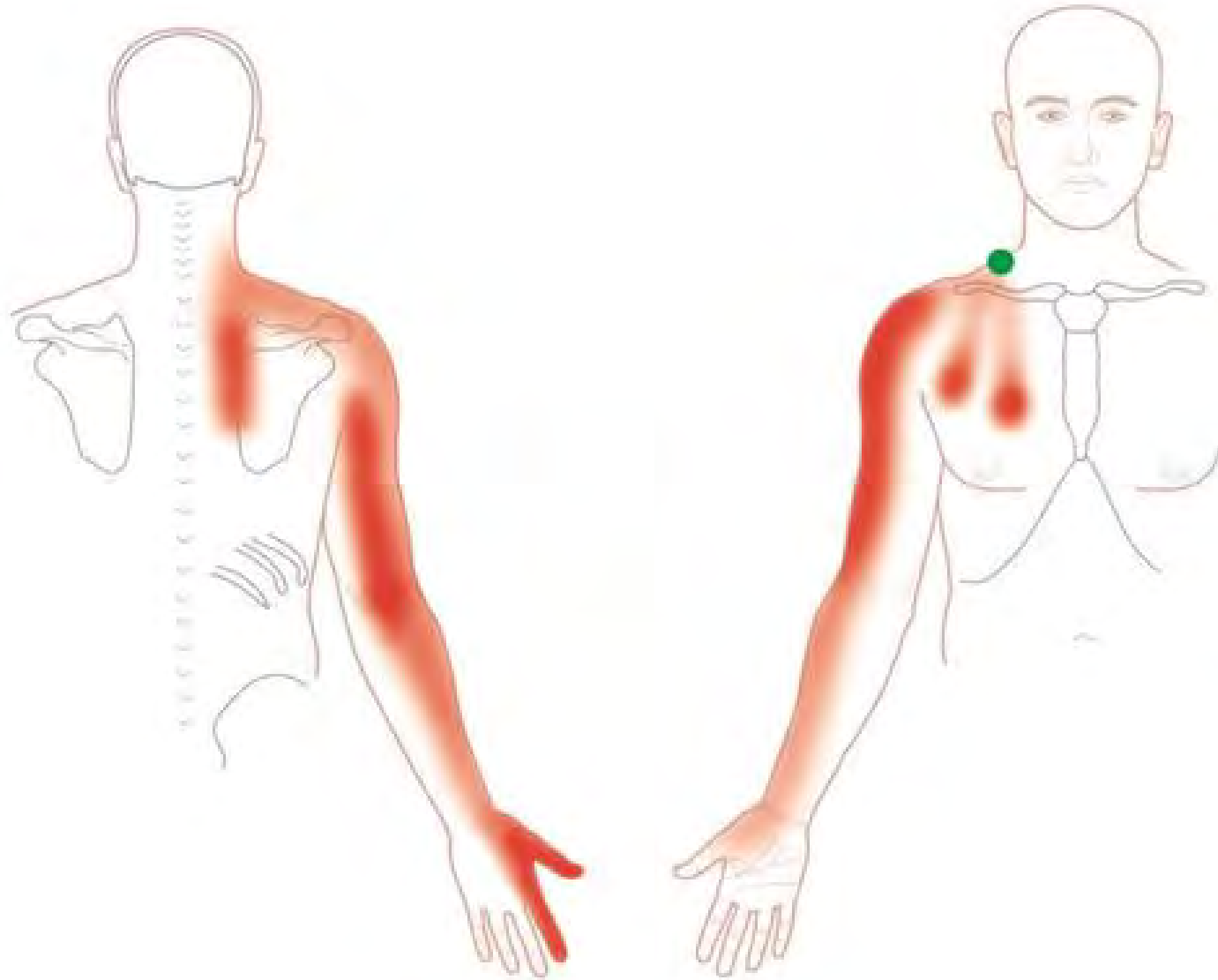
Pain in arms

- Shoulder joint subluxations, dislocation
- Thoracic outlet syndrome
- Elbows: Tendonitis, bursitis, hyperextension
- Wrist and fingers: subluxations, muscle pain, tendonitis

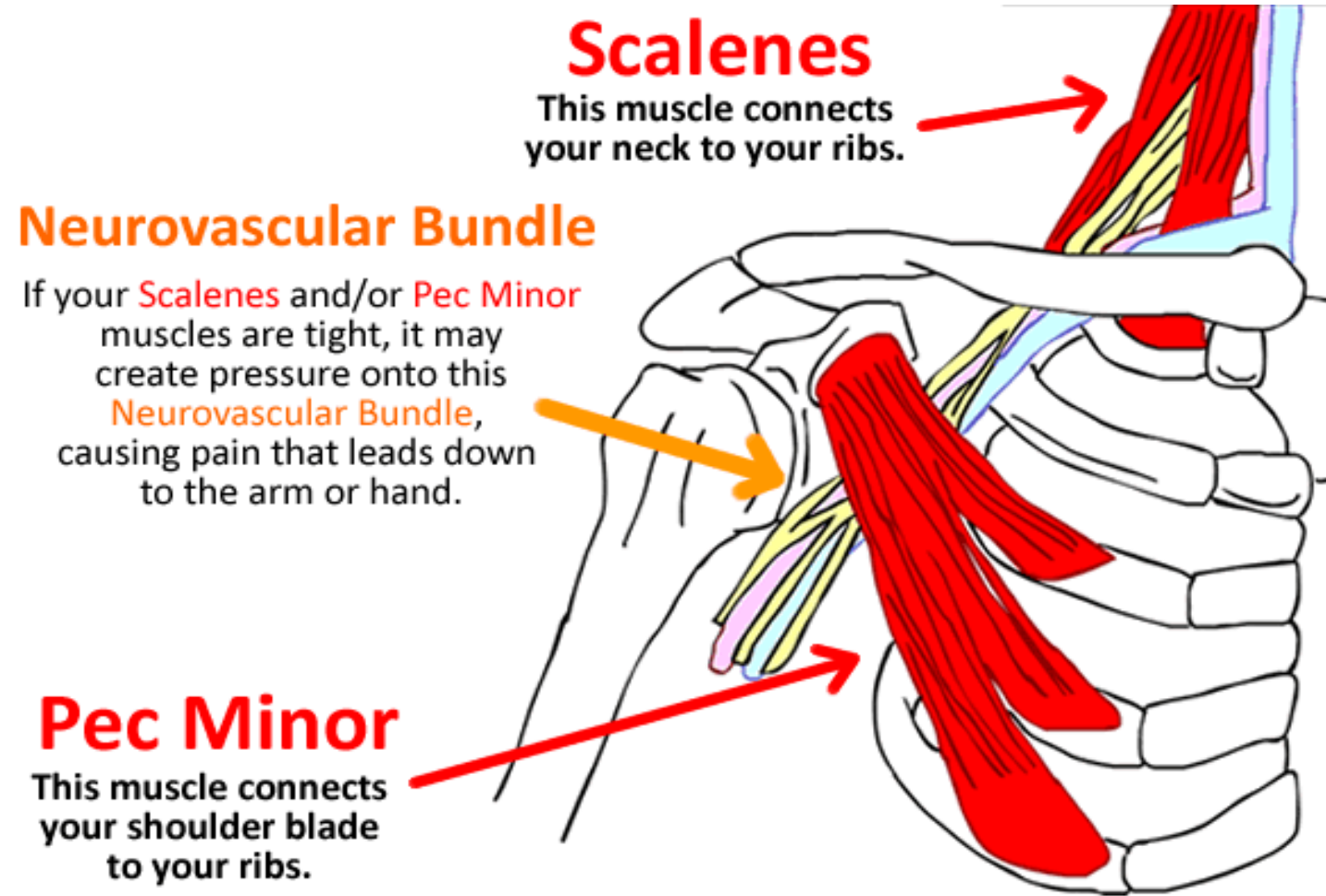
Shoulder pain

- Laxity of the shoulder joint causes the muscles (rotator cuff) around the shoulder to spasm
- Thoracic Outlet syndrome.

Pain patterns in Thoracic Outlet syndrome



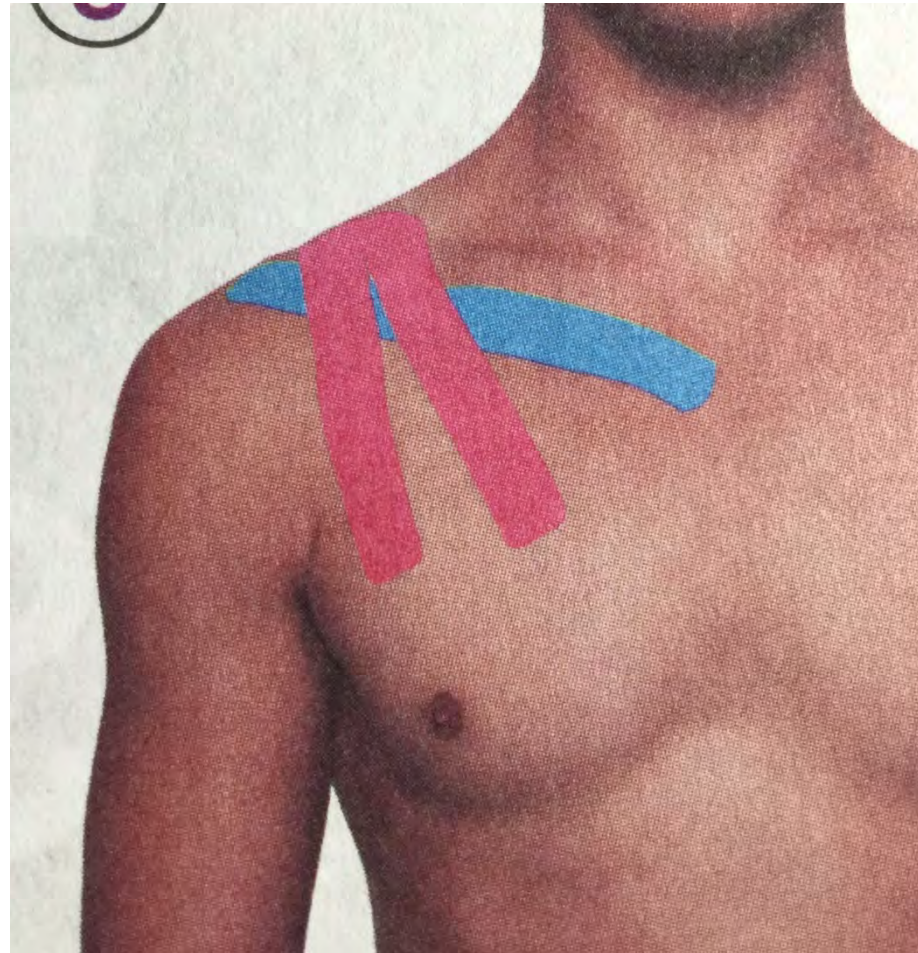
Thoracic Outlet Syndrome



Thoracic Outlet Syndrome

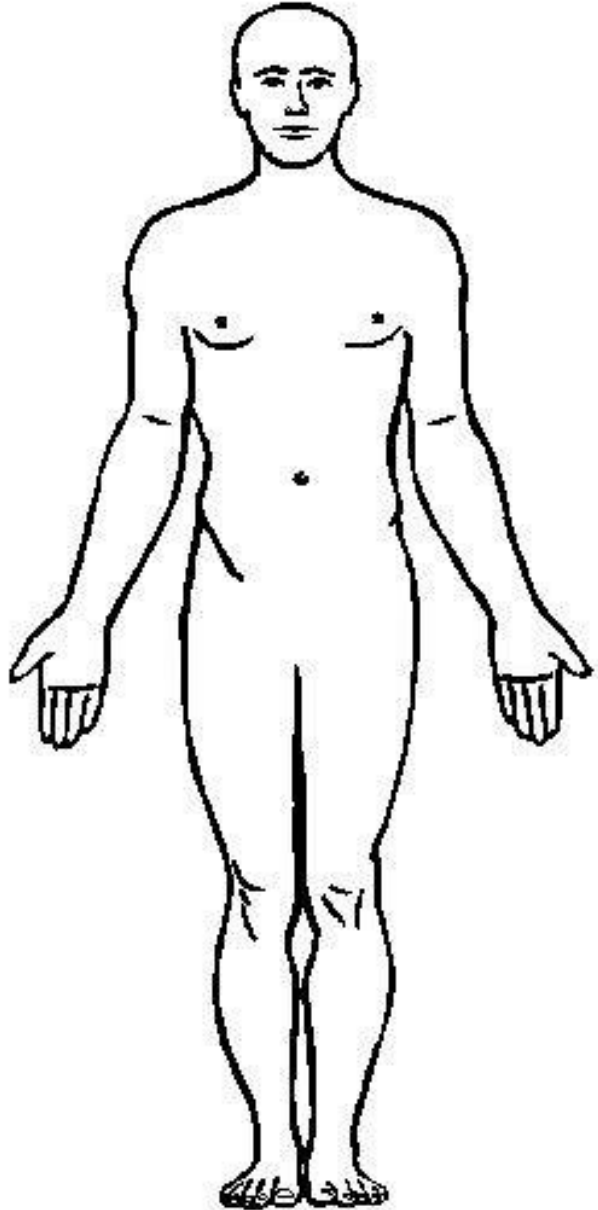
- Physical therapy
- Kinesio taping
- Botox injections
- Surgical correction

Kinesio Taping for shoulder joint pain



Wrists and fingers

Hand and wrists



Muscles of the hand

- In EDS, patients tend to grip objects tightly to compensate for poor proprioception
- Small intrinsic muscles of the hand fatigue easily



The EDS way of holding a pen

- Poor proprioception makes patients grip a pen with as many fingers as possible
- They hold the pen very tight and press down hard on paper
- Puts abnormal pressure on the muscles and joints of the hand and wrist



- Dense foam padding (Ableware®) or wrap a foam padded tape – for pens, tooth brush, forks, knives



- Compression half finger gloves
- Brace for unstable joints



Splints for fingers

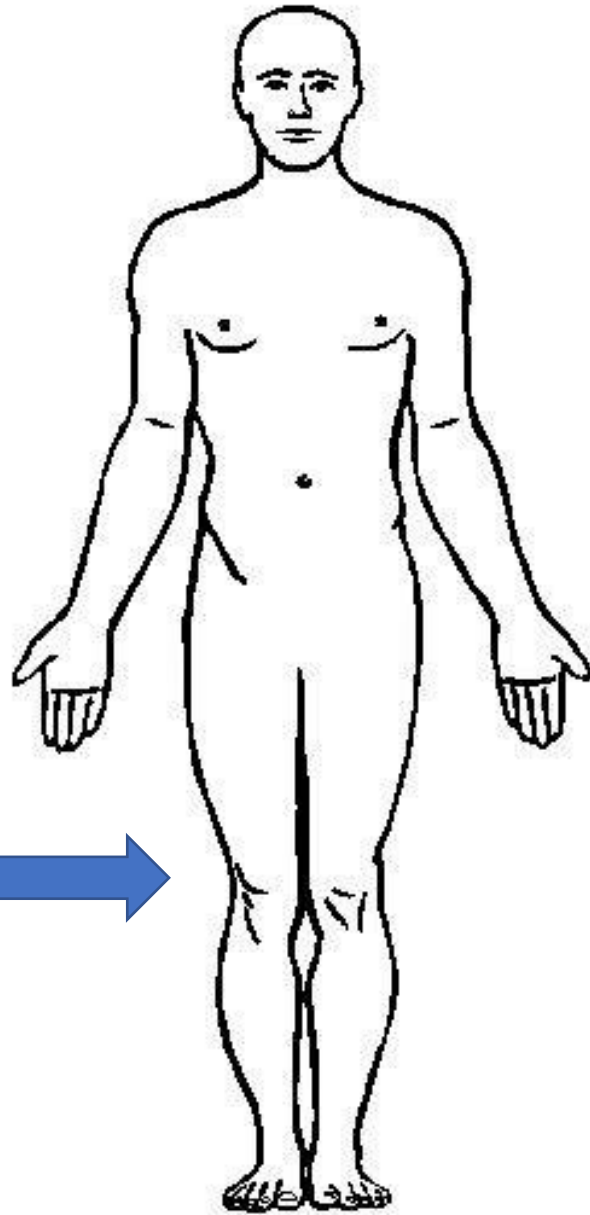


Splinting and braces in general

- Braces maintain joint in neutral position
- Avoid hyper – extension
- Braces help with joint position awareness (proprioception)
- Start using them gradually
- Gradually decrease their use as you gain strength
- Kinesio taping is a good option

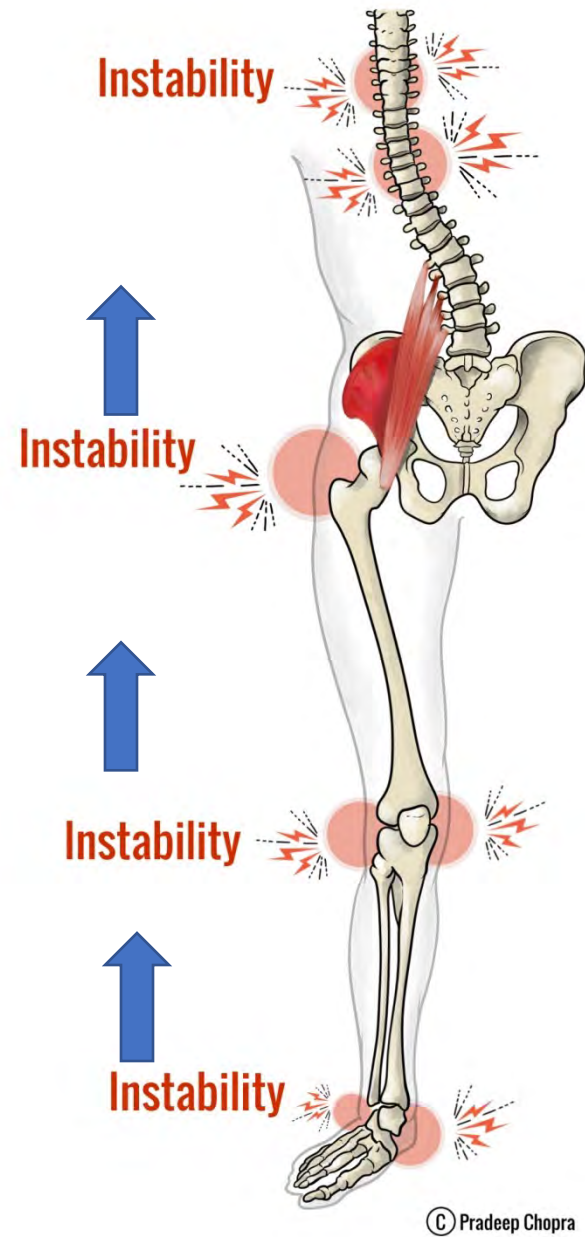
Legs in Ehlers Danlos Syndromes

Legs and knees

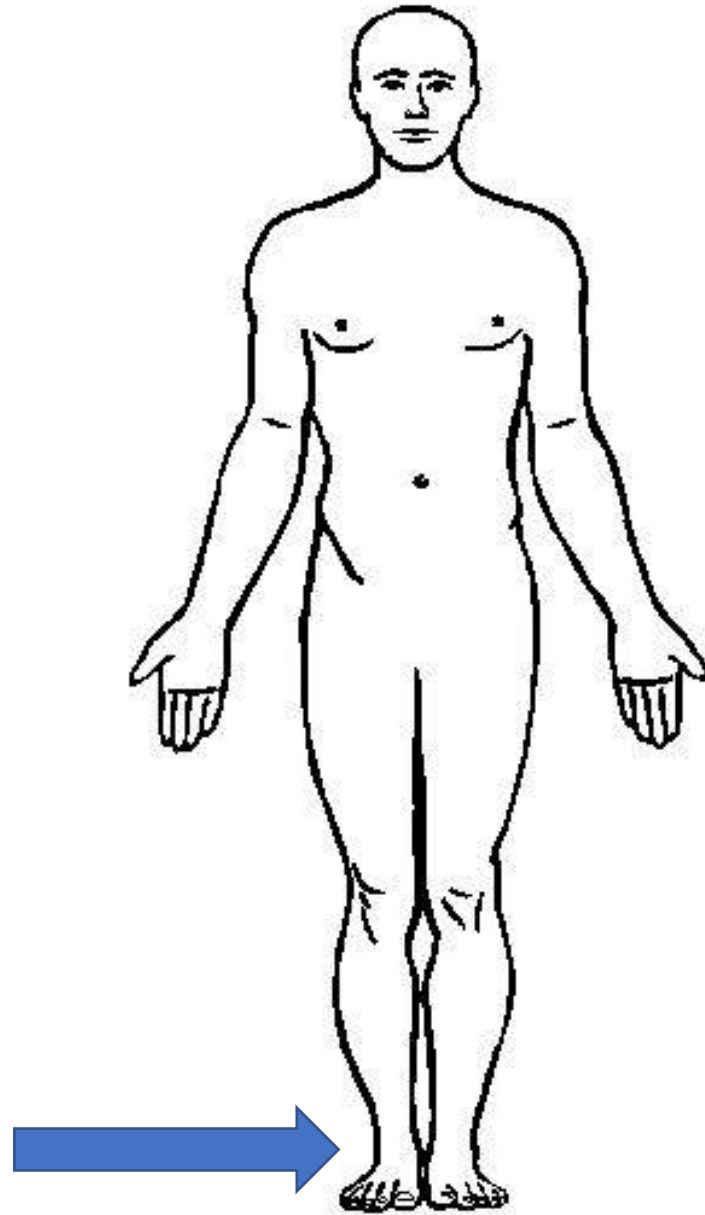


Pain in lower half of the body

- If the feet and ankles are unstable, they make
- The knees even more unstable, which then
- Makes the hips unstable, which then
- Throws the pelvis and spine off



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Ankles and feet

Flexible flat feet – predominantly in the forefoot



Over-Pronation ankles usually associated with flat feet



Weight evenly distributed

Weight shifts to the inside of the sole

Left Foot



Normal Foot

**Flat Foot
(excessive pronation)**

The feet in EDS

- Barefoot walking, where safe and comfortable – helps with conditioning of muscles under natural loads
- Repeated rising on tip toes – strengthens the muscles in foot and with proprioception
- Ankle raises by lifting heel (not leaning forward)
- Descend in a slow controlled way

Footwear - shoes

- Extremely important to wear proper footwear
- Help with unstable ankles, hypermobile feet
- Cushioned mid sole
- Good, strong heel counter provides stability
- Fastenings should be over the mid-sole for better support
- Sneakers !!

Orthotics

- Custom made orthotics
- Start using them slowly – one hour a day for a few days, two hours a day for a few days.....
- Give your feet a chance to adjust



Ankle brace to stabilize the ankle joint



Knees

Patella is stabilized muscles of the thigh



- A hypermobile patella can make the knee unstable
- It causes pain in the muscles that support the patella

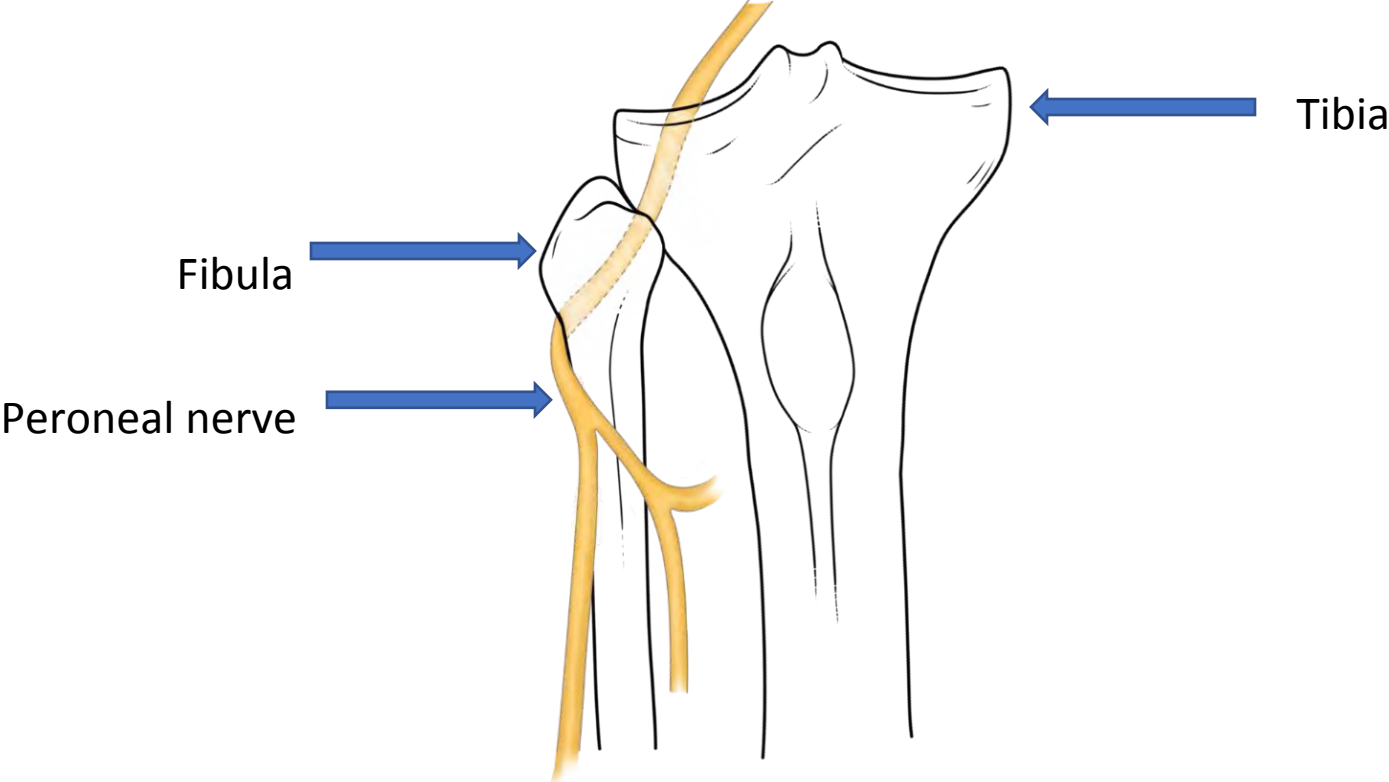


Treatment options for knee pain in EDS

- Stabilize the feet and ankles, first
- Strengthen muscles around the knee
- Knee brace

A missed cause of leg pain – the proximal tibio fibular joint

Proximal Tibio-Fibular joint

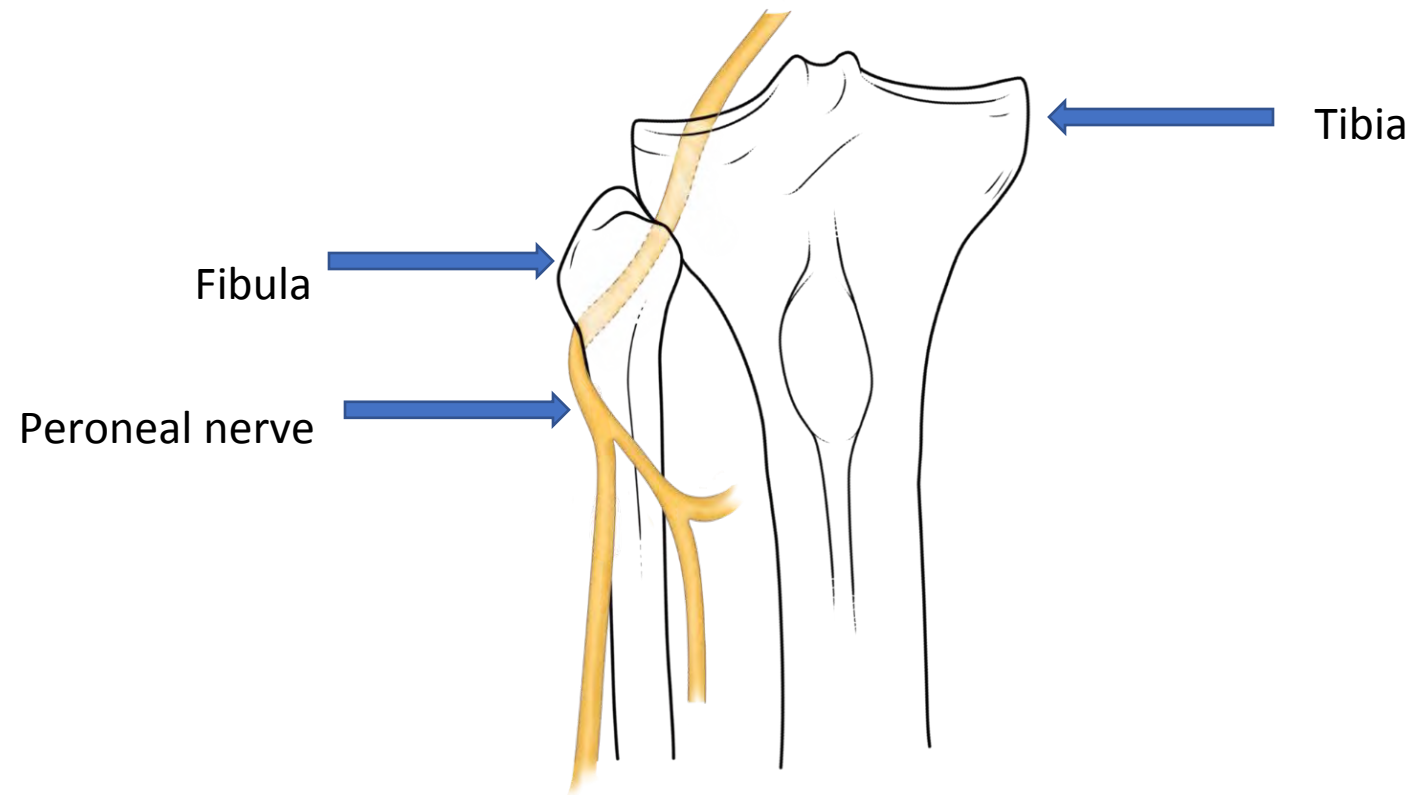


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Knee pain – often missed cause of pain in the leg

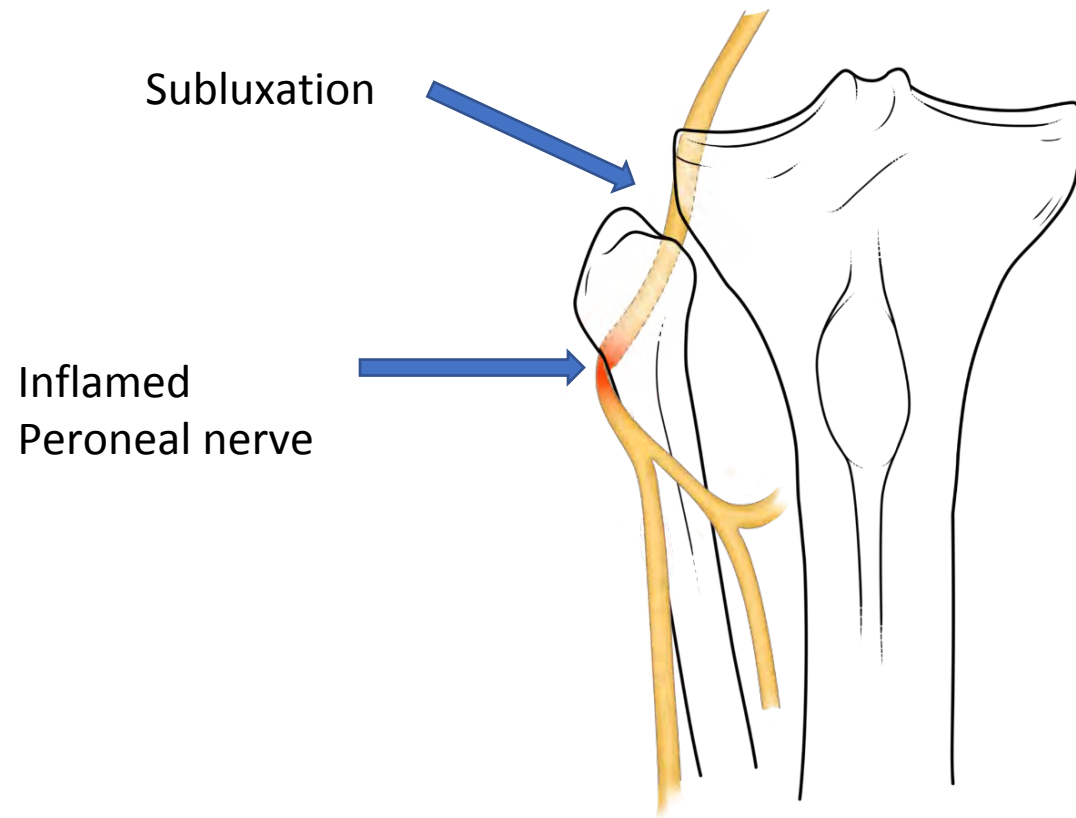
- The proximal tibio-fibular (PTF) joint is on the outside of the knee.
- Like all joints it is prone to subluxations or arthritis.
- A subluxing PTF joint affects the Peroneal nerve, which affects the side of the leg and causes pain in the leg and foot drop

Proximal Tibio-Fibular joint



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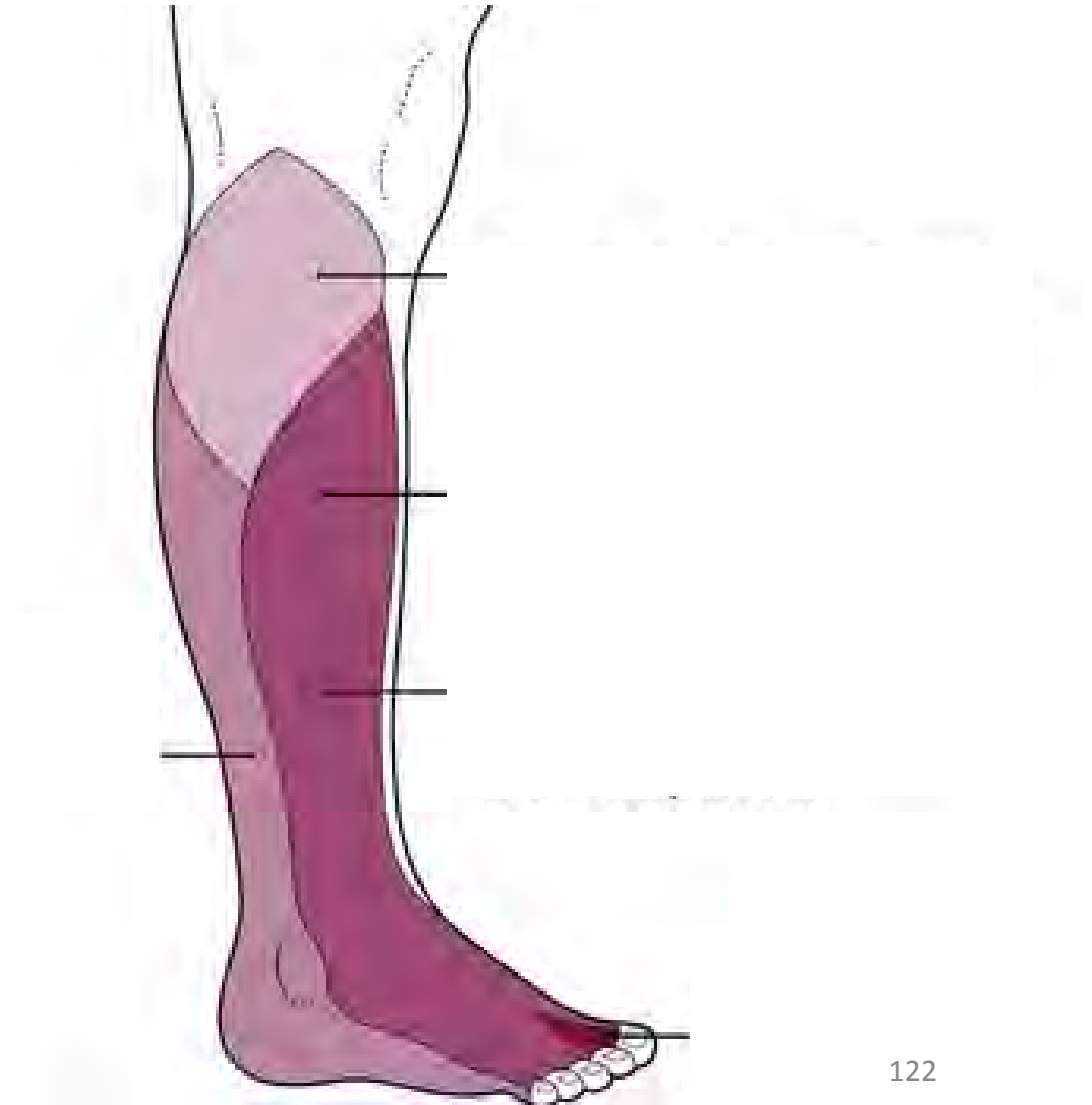
Proximal Tibio-Fibular joint



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Knee pain – often missed cause

- Site of pain from the proximal Tibiofibular joint
- It can inflame the peroneal nerve which causes pain down the side of the leg and even foot drop



Knee stabilizing brace



Ilio Tibial band (Fascia Lata Fasciitis)

- Pain on the side of the thigh up to the knee
- It is usually because of an unstable Sacroiliac joint (SIJ), knee or hip joint
- IT band connects to the lateral retinaculum to the patella
- The IT band is tightened in subluxation of the PTF and hypermobile patella
- Treat the knee or hip problem
- Stretching the IT band may not help



Dysautonomia / POTS (Postural Orthostatic Tachycardia Syndrome)

Postural Orthostatic Tachycardia syndrome (POTS) - Symptoms

- Fainting, dizziness
- Heart racing (Palpitations)
- Fatigue
- Headaches
- Cold hands and feet
- Poor concentration “brain fog”
- Feeling of constant anxiety

POTS - Postural Orthostatic Tachycardia syndrome - diagnosis

- Increase in heart rate by 30 beats/min within 10 minutes of standing
- heart rate of 120 beats / min within the first 10 minutes of standing
- No significant change in blood pressure
- Syncope or almost syncope (fainting)
- In children an increase of 40 beats/minute

POTS - tests

- Orthostatics – Measure blood pressure and heart rate while lying down, standing up for 10 minutes - preferred
- Tilt table test

Diagnosis of POTS



120/80

70



Increase in heart rate by 40 beats/minute with very little change in blood pressure

Standing Immediately



118/78

110



Standing for 10 minutes



122/80

105

Treatment of POTS

- Increase oral salts
- Increase oral electrolyte fluids
- Compression tights up to thighs.
- Abdominal binder (wear swim suit 1 size smaller)
- Cardiology consult for Dysautonomia/POTS.

POTS - Postural Orthostatic Tachycardia syndrome

Consult Dysautonomia International for more information and high salt diet recipes.

<http://www.dysautonomiainternational.org/>

- The constant feeling of dizziness makes patients feel unstable
- The laxity of the joints makes the muscles tighten reflexly
- This constant use of muscles worsens their pain and fatigue

Mast Cell Activation Syndrome

MCAS

Mast cells

- Cells in blood
- Normally present in blood
- Contain histamine, cytokines and a bunch of other chemicals
- Involved in allergy, wound healing and protection against infection

EDS, POTS and MCAS

A New Disease Cluster: Mast Cell Activation Syndrome, Postural Orthostatic Tachycardia Syndrome, and Ehlers-Danlos Syndrome

Cheung, Ingrid, Vadas, Peter

Journal of Allergy and Clinical Immunology , Volume 135 , Issue 2 , AB65, February 2015

Mast Cell Activation Disorder (MCAD)

- In Ehlers Danlos Syndrome, mast cells are normal in count (not increased)
- Hyper-reactive
- May not have a specific trigger that makes the mast cells release histamine

Mast Cell Activation Syndrome (MCAS)

- MCAS is a large, prevalent collection of illnesses resulting from mast cells which are inappropriately activated but are NOT significantly proliferated (different from Mastocytosis).
- Increased mast cell activity in CRPS (Birklein, 2014)

Mast Cell Activation Syndrome (MCAS)

- Rashes, hives, itchy
- Fatigue, tiredness
- Muscle pain
- Bone and joint pain
- Abdominal pain, bloating, nausea
- Racing heart beat, almost fainting,
- Flushing especially after a hot shower
- Bladder problems – interstitial cystitis

Mast Cell Activation Syndrome (MCAS)



<https://mastcellblog.wordpress.com/mastcell/>

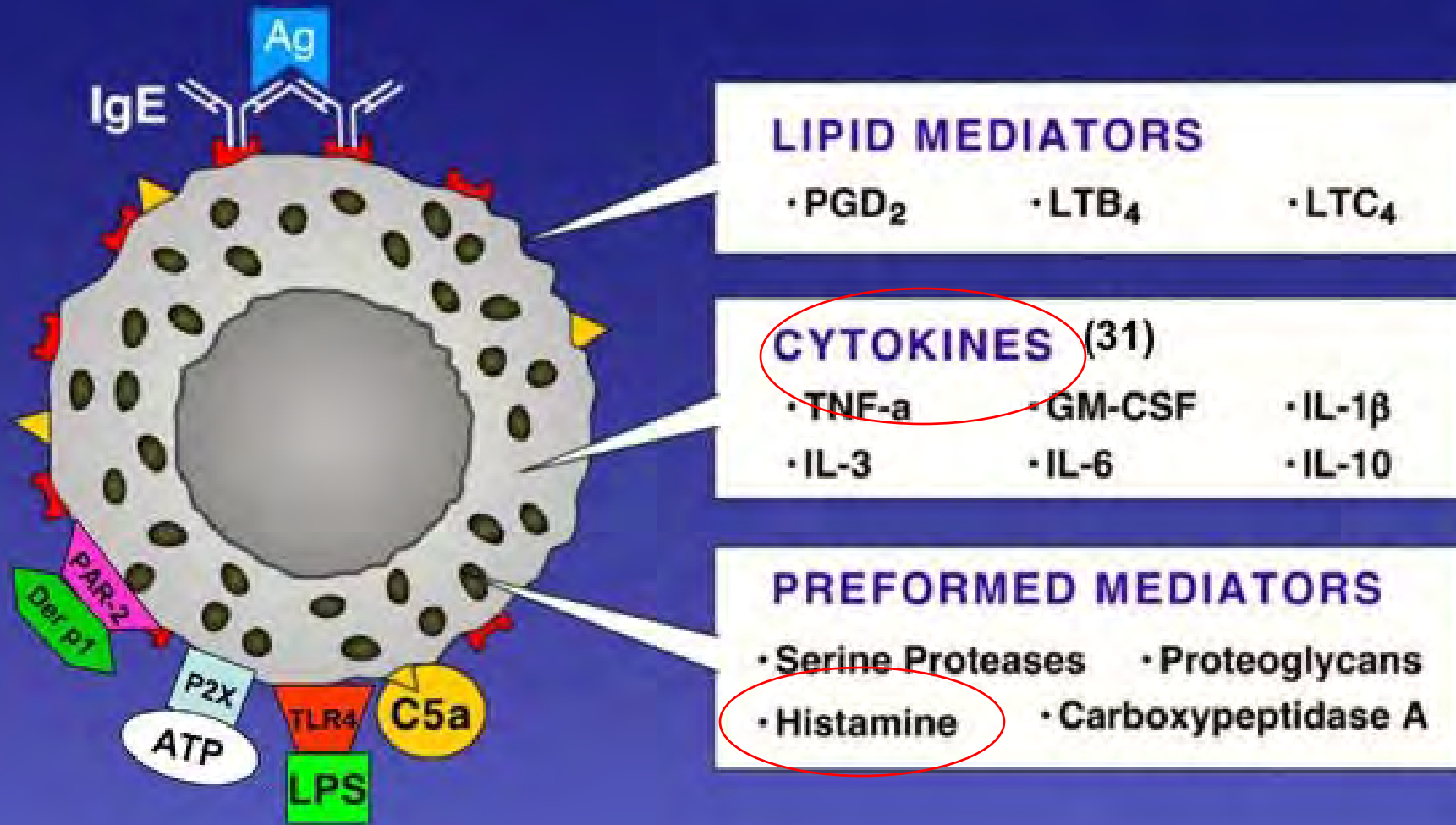
Pradeep Chopra, MD

Mast Cell Activation Syndrome (MCAS)

- Temperature instability – hot / cold
- Multiple chemical sensitivities – food, drugs,
- Sensitivities to multiple drugs maybe due to fillers – changing to a different brand may help
- Dry eyes, difficulty focusing,
- Hair loss
- Bladder pain: Interstitial cystitis – inflammation of bladder

MC

MEDIATORS RELEASED FROM ACTIVATED MAST CELLS



Symptoms of EDS, POTS, MCAS

Headaches, brain fog, dizzy →

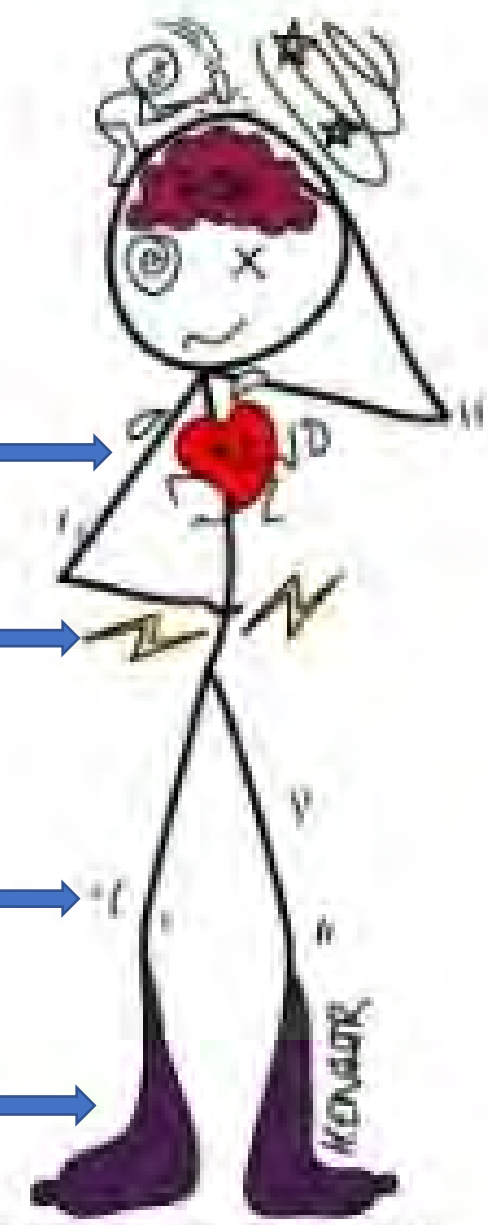
Blurry vision →

Racing heart →

Belly pain →

Tremulousness →

Dark discoloration of feet →



stickmancommunications.co.uk

Management of MCAS

- Anti-histamine drugs:
 - Most cold medicines
 - Ranitidine, famotidine
- Cromolyn
- Low histamine diet
 - avoid: sudden change in temperature, certain seasonings (except olive oil and salt)
 - Certain foods may increase MCAS: seasonings, beef, gluten, most grains (except quinoa and rice)

Fatigue in EDS

Non Ehlers Danlos Syndrome

- Muscles – relaxed at rest and contract with activity
- Ligaments – tensed at rest, they support and stabilize the body

Ehlers Danlos Syndrome

- Muscles – They are tensed and constantly attempt to stabilize even at rest
- Ligaments – provide no tension and stability

Fatigue in EDS

- There are many reasons for fatigue in EDS
- EDS –
 - muscle fatigue from constant tightness to compensate for lax ligaments,
 - primary muscle weakness (myopathy)
- POTS – compensated circulation, constant instability from dizziness

Fatigue in EDS – some more causes

- MCAS (Mast Cell Activation Syndrome) – histamine and cytokines.
- Poor sleep
- Medications

Fatigue in EDS

- Stimulating the nervous system with amphetamine may not be the best choice
- Correct the underlying cause.
- Combination of ubiquinone and L-Carnitine
- Frequent breaks, do not push through fatigue
- Adequate hydration



Children and chronic pain

- It is often labeled as a behavioral disorder, conversion disorder and parents are labeled as having Munchausen's syndrome
- Very important that parents pay close attention to the child's complaints.
- Trust your child your own instincts. A mother knows her child best



Behavioral

- The diagnosis of Conversion Disorder or Munchausen by Proxy are often made by providers with little training in Psychiatry and vice versa most psychiatrists have no training in pain conditions.

1 Marsden CD. Hysteria: a neurologist's view. *Psychol Med*. 1986;16:277-88

2. R J McClure, P M Davis, S R Meadow, and J R Siber. Epidemiology of Munchausen syndrome by proxy, non-accidental poisoning, and non-accidental suffocation. *Arch Dis Child*. 1996 Jul; 75(1): 57-61.



Behavioral

- To diagnose a child with Conversion disorder or Munchausen by Proxy without a dedicated multidisciplinary team approach and without concrete evidence is extremely harmful to the patient.

Breathing

- Playing a flute or singing is helpful for improving proprioception in the lungs and chest.
- It helps build nerve connections between the diaphragm ribs and chest wall muscles.
- It helps with the sensation that you have to catch your breath or feel short of breath.
- It also helps strengthen core muscles – using the diaphragm to blow air requires using muscles of the stomach and back.
- Using a flute helps with proprioception of the fingers and wrists – it helps build the brain to joints of the hands connection

Service Dogs - invaluable

- POTS – they can sense when their owner is having an episode of dizziness or seizure
- EDS and pain - they protect the limb from being injured or touched
- Helps boost confidence in their owners, making them more independent
- Help with balance, call for help, open doors, switch on lights, pull wheelchairs, anxiety,

The Feldenkrais Method

- It is a type of physiotherapy that helps repair impaired connections between the brain and the body
- Patients with EDS develop inefficient or strained habitual movement patterns
- The Feldenkrais Method teaches new patterns using gentle, slow, repeated movements.
- It uses slow repetition to teach correct and safe movements in EDS

The Feldenkrais Method

- It is based on principles of physics, biomechanics and an understanding of learning and human development.
- This method of exercise is excellent for improving proprioception in Ehlers Danlos Syndrome.
- Can be done sitting or lying down
- Each session consists of comfortable, easy movements within the limits of safety

Medicinal marijuana

- The human body has two types of receptors – CB1 and CB2
- CB1 receptors are found in the brain
- CB2 receptors are found in the rest of the body, immune cells and glia cells in the Central Nervous System
- Chemicals that cause inflammation in the peripheral parts of the body are modulated by cannabinoids. Hence, cannabis applied topically may be helpful

Medicinal Marijuana

- MM basically contains 2 substances – THC and CBD
- THC works on CB1 and is responsible for the cognitive effects
- CBD works on CB2 and is responsible for pain relief, helps autoimmune dysfunction.
- For MM to work, both THC and CBD have to be together, separating them is not as effective. This is called the Entourage effect.
- One can take MM with a higher concentration of CBD and lower concentration of THC – for pain
- Higher THC and lower CBD for sleep

Cannabis

- Cannabis can reduce the migration of inflammatory chemicals to the site of injury and into the brain.
- This is especially important because in immune dysfunction, migration of inflammatory cells into tissues and nervous system contributes to neuropathic pain

Medicinal Marijuana

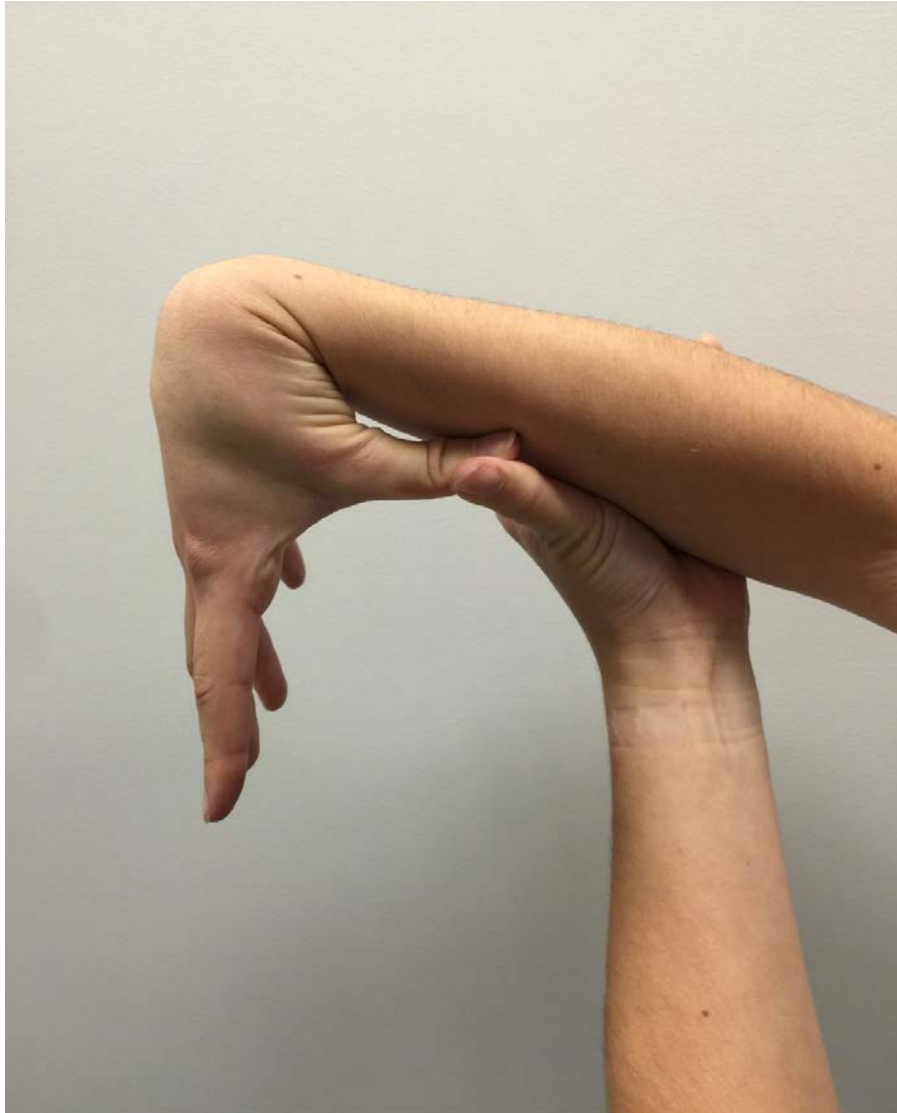
- Reasonable choice to try.
- Anecdotally – works well in patients with EDS
- Higher CBD levels and lower THC levels
- Vaporizing, edibles
- Topical over joints and muscles.
- Does not affect Mast Cell Activation Syndrome (MCAS) as much as NSAID's and opioids

The Beighton Score

The Beighton Score

- Score 1 point for each joint.
- Maximum 9 points
- No definite cut off for diagnosis of EDS
- In general, a score of 4 or 5 out of 9 should trigger suspicion of EDS

2. Beighton score - Passive apposition of the thumb to the flexor aspect of the forearm



4. Beighton Score: Passive dorsiflexion of the 5th finger beyond 90 degrees



6. Beighton Score: Hyperextension of the elbow



8. Beighton Score: Hyperextension of the knees



9. Beighton Score: Forward flexion of the trunk with the knees extended and the palms resting flat on the floor



Other signs to look for

Posture when sitting



Namaste sign



Diagnosis of EDS (Hypermobile) in adults – the 5 point questionnaire

1. Can you now or could you ever place the your hands flat on the floor with out bending your knees?
2. Can you now or could you ever bend your thumb to touch your forearm?
3. As a child did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager, did your kneecap or shoulder dislocate on more than one occasion?
5. Do you consider yourself double jointed?

Positive if the answer is yes to 2 or more questions

Complex Regional Pain Syndrome (CRPS)

What is CRPS / RSD

- Syndrome characterized by a continuing pain that is disproportionate to the usual course of any trauma or lesion.
- Usually starts after a trauma

Cause of CRPS

- Although by definition CRPS does not have a known cause
- Its just that we have not found the cause
- But what if we can identify a cause?

Diagnosis of CRPS

Signs and Symptoms of CRPS 1

- Pain starts in one limb but can present in the trunk (spine, abdomen, pelvis)
- Constant pain, even at rest with intermittent exacerbations.
- Temperature differential
- Color differential – comes and goes
- Swelling – comes and goes
- Area of pain larger than the primary injury

Signs and Symptoms of CRPS

- Pain or uncomfortable sensation to touch
- Nail growth changes (faster, distorted),
- hair growth changes (coarser, darker, rapid growth, hair falling),
- skin changes – thin and shiny
- skin lesions – pin point lesions to blisters
- Increased sweating



Swelling

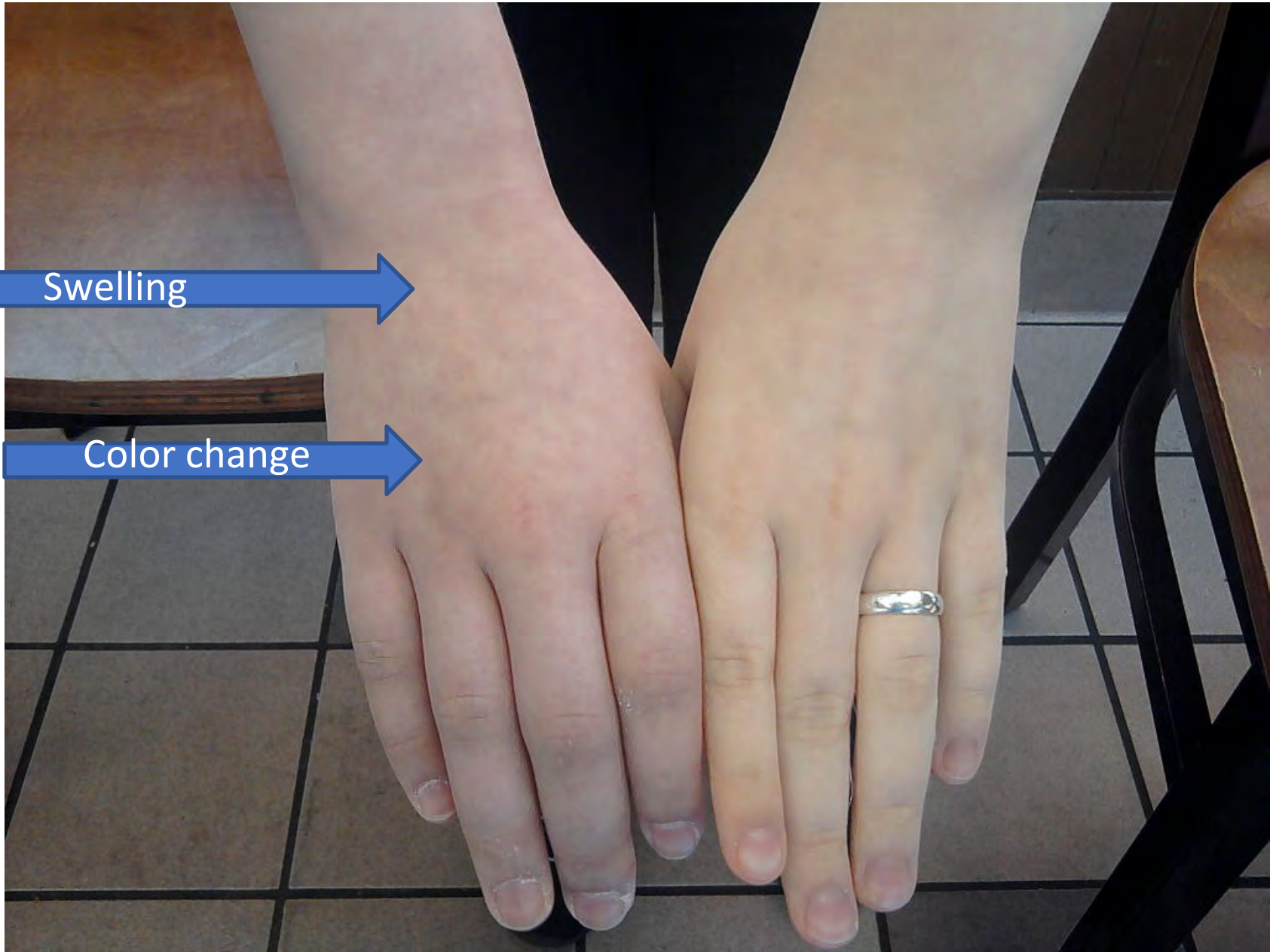
Color
change



Swelling

Shiny skin

Nails growth faster,
brittle, ridged



Tests that are not helpful for diagnosing CRPS

- Imaging techniques – x-ray, MRI, fMRI, Three phase bone scan, bone density
- Blood tests
- Skin biopsy
- Sympathetic nerve tests – sweat test, sympathetic skin response,
- Nerve tests – EMG, nerve conduction,
- The tests MAYBE used if another diagnosis is suspected.

Atkins RM, Tindale W, Bickerstaff D, Kanis JA. Quantitative bone scintigraphy in reflex sympathetic dystrophy. Br J Rheumatol 1993;32(1):41-5.

Todorovic-Tirnanic M, Obradovic V, Han R, Goldner B, Stankovic D, Sekulic D, et al. Diagnostic approach to reflex sympathetic dystrophy after fracture: radiography or bone scintigraphy? Eur J Nucl Med

Best Diagnostic tool

- A good history and thorough physical examination
- The diagnosis of CRPS is clinical and not based on any test or procedure

CENTRAL SENSITIZATION

Key concept to understanding all chronic pain

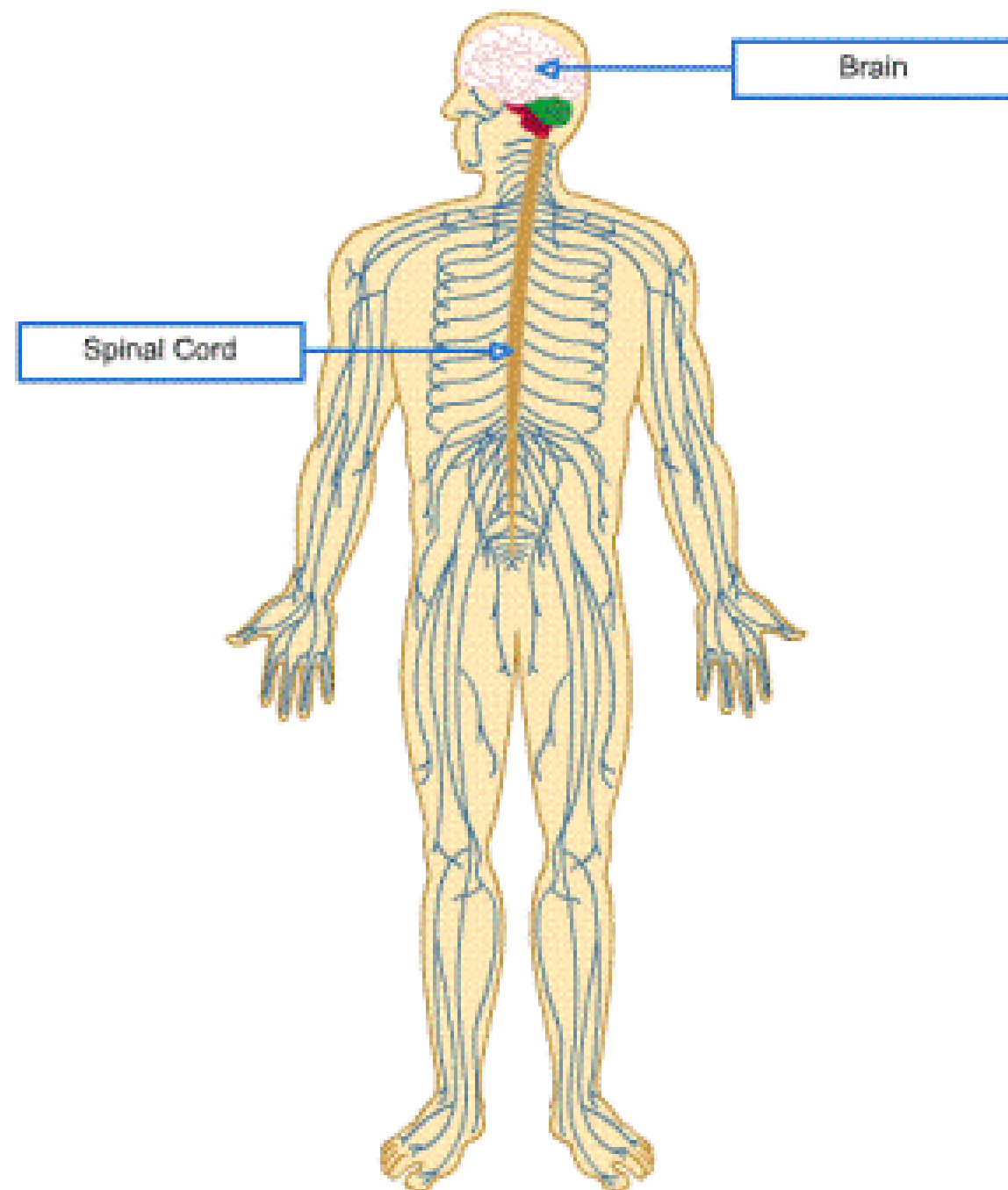
Central Sensitization

- A normal sensation (e.g. touch) produces an abnormal response (like pain) because the brain and spinal cord are sensitized
- Definition: Increase in the excitability of neurons within the central nervous system (CNS) so that normal inputs produce abnormal responses

Central Nervous System

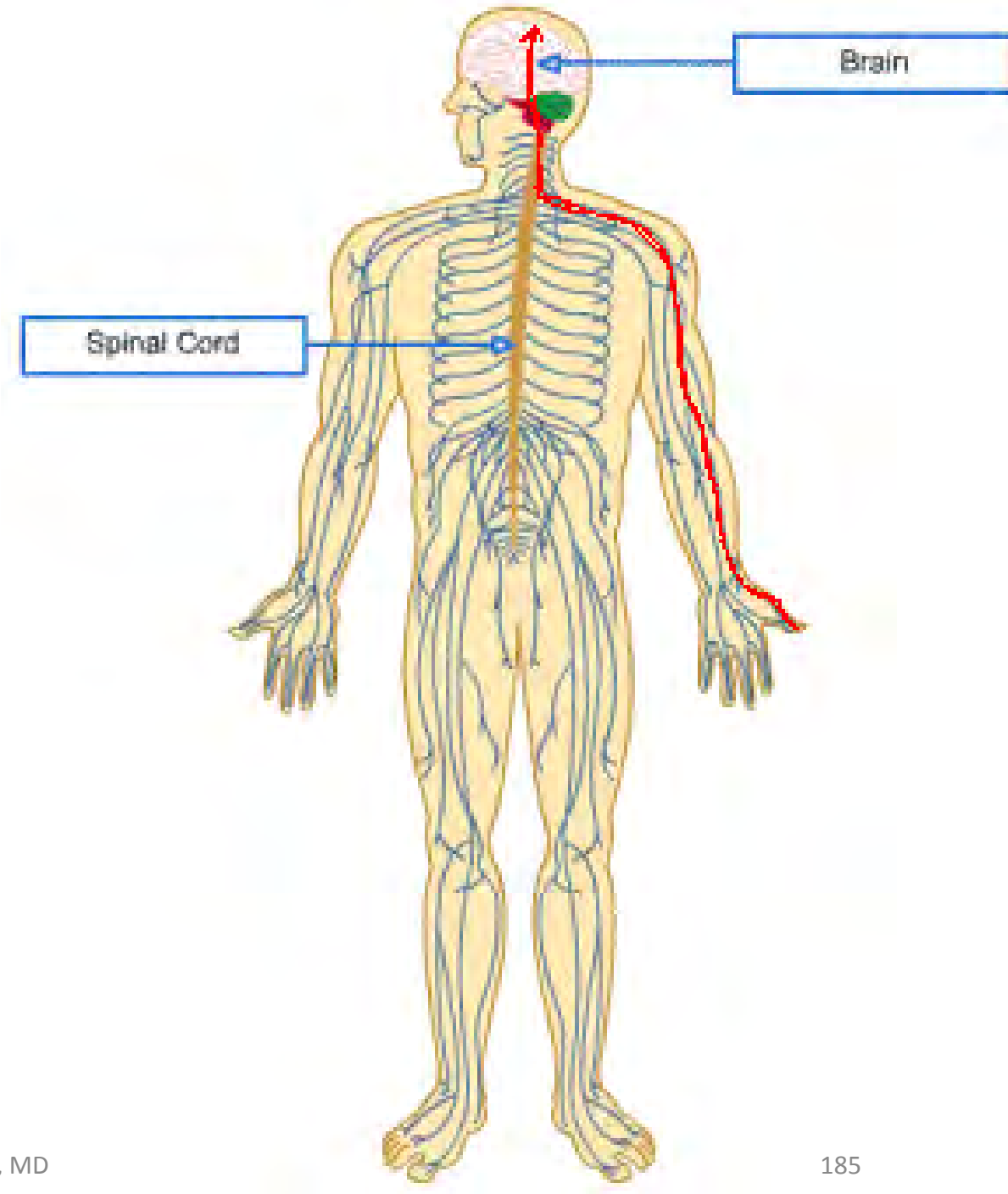
- The Central Nervous system (CNS) is made of 2 parts:

1. Brain
2. Spinal cord



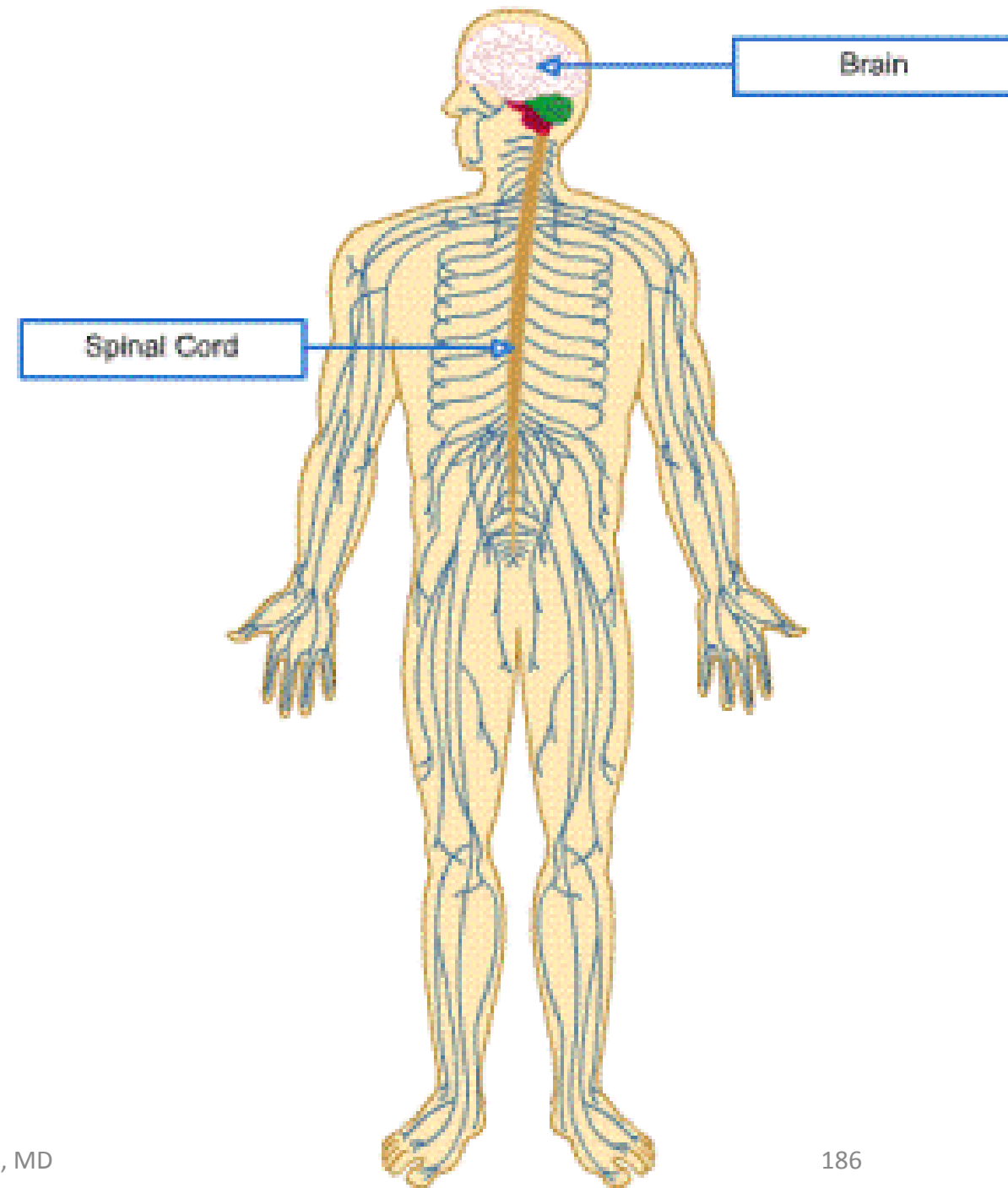
Normal pain

- Normally, an injury will cause pain and the signals are sent to the brain
- In the brain, the signal gets an emotional component and we sense pain



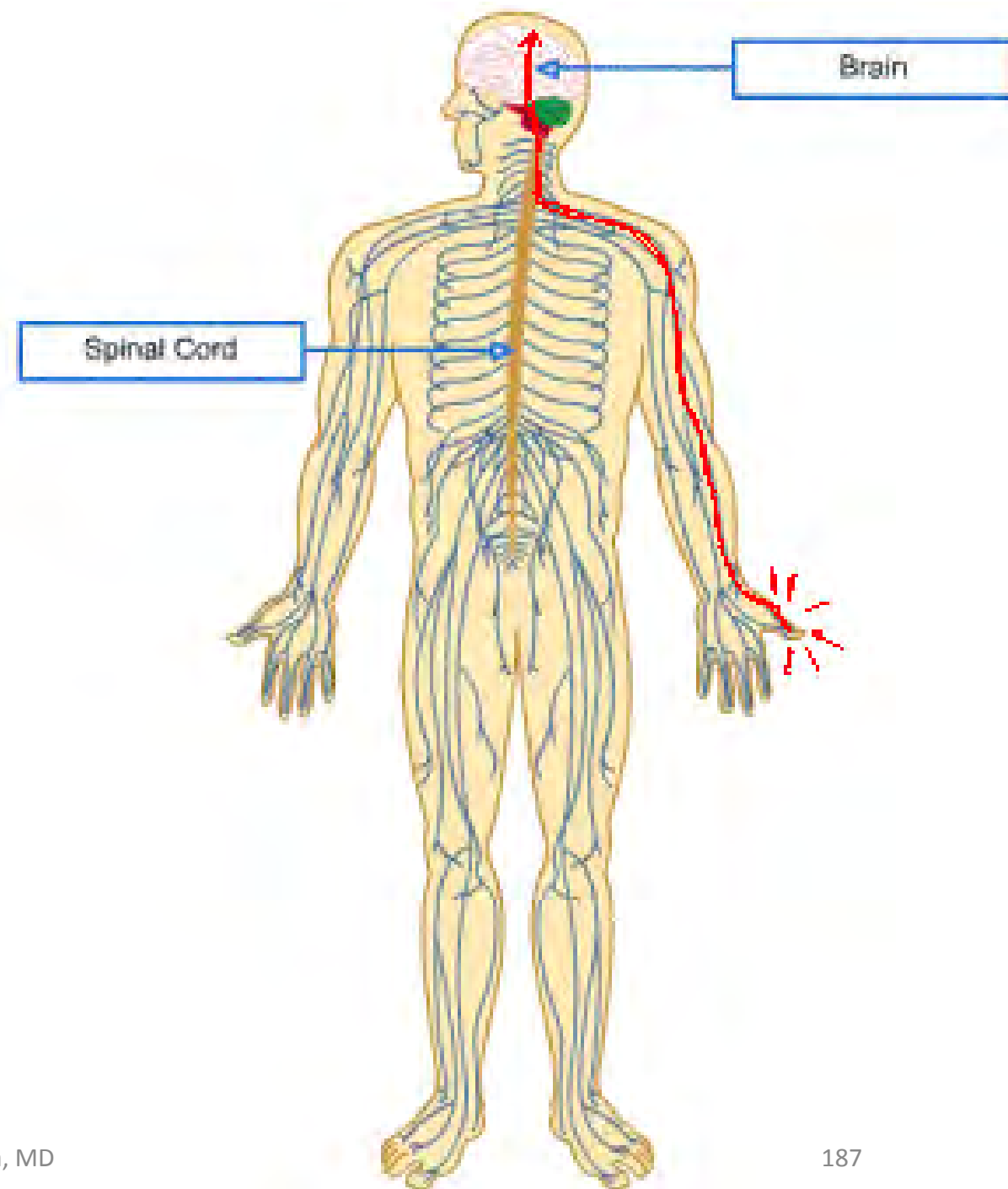
Normal pain

- Once the injury heals, the signals stop and everything returns to normal



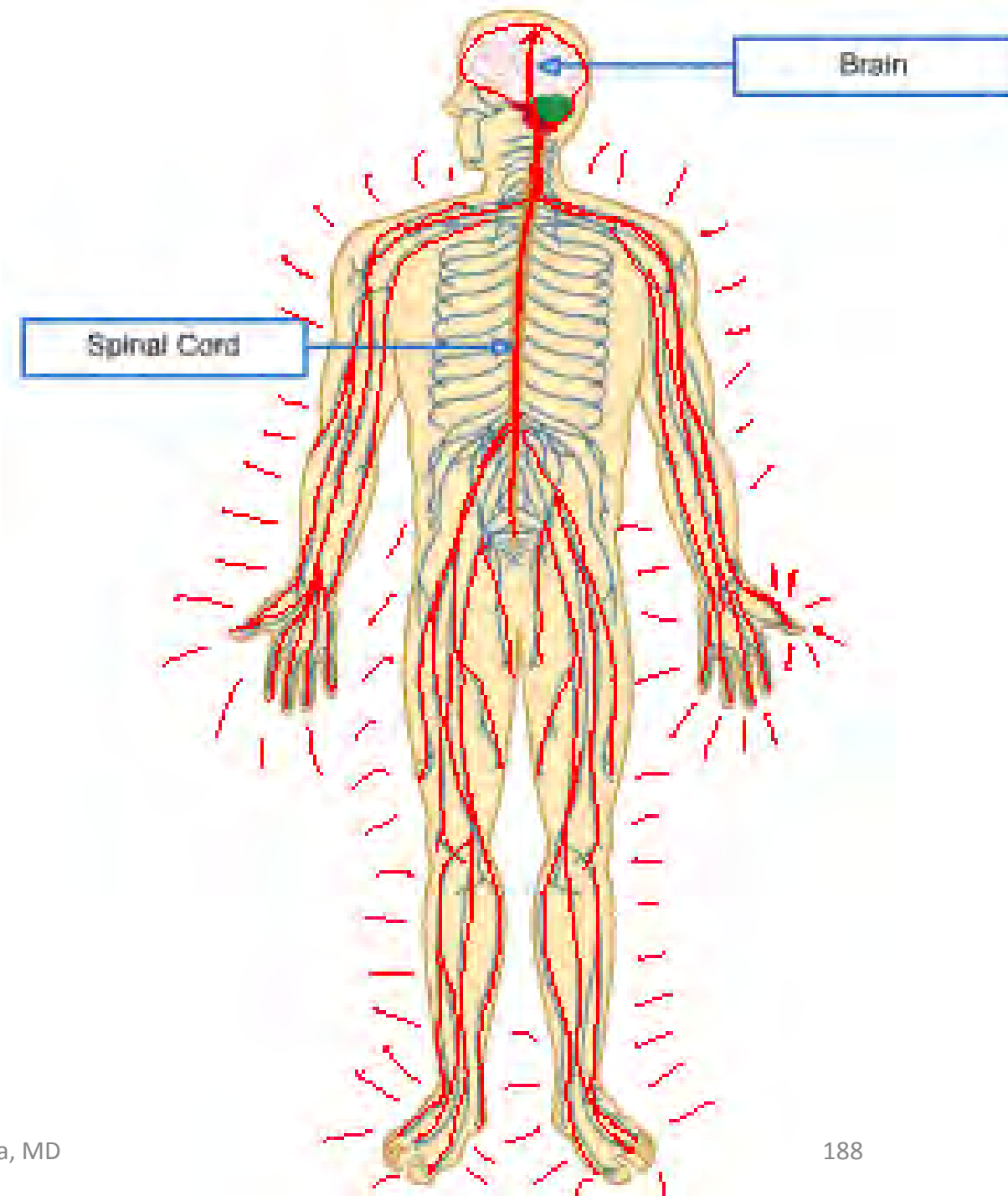
CRPS

- In CRPS, the pain signals continue even after the injury heals
- The brain also tries to send signals down to suppress the pain signals
- In CRPS, there is a constant barrage of pain signals travelling up and down



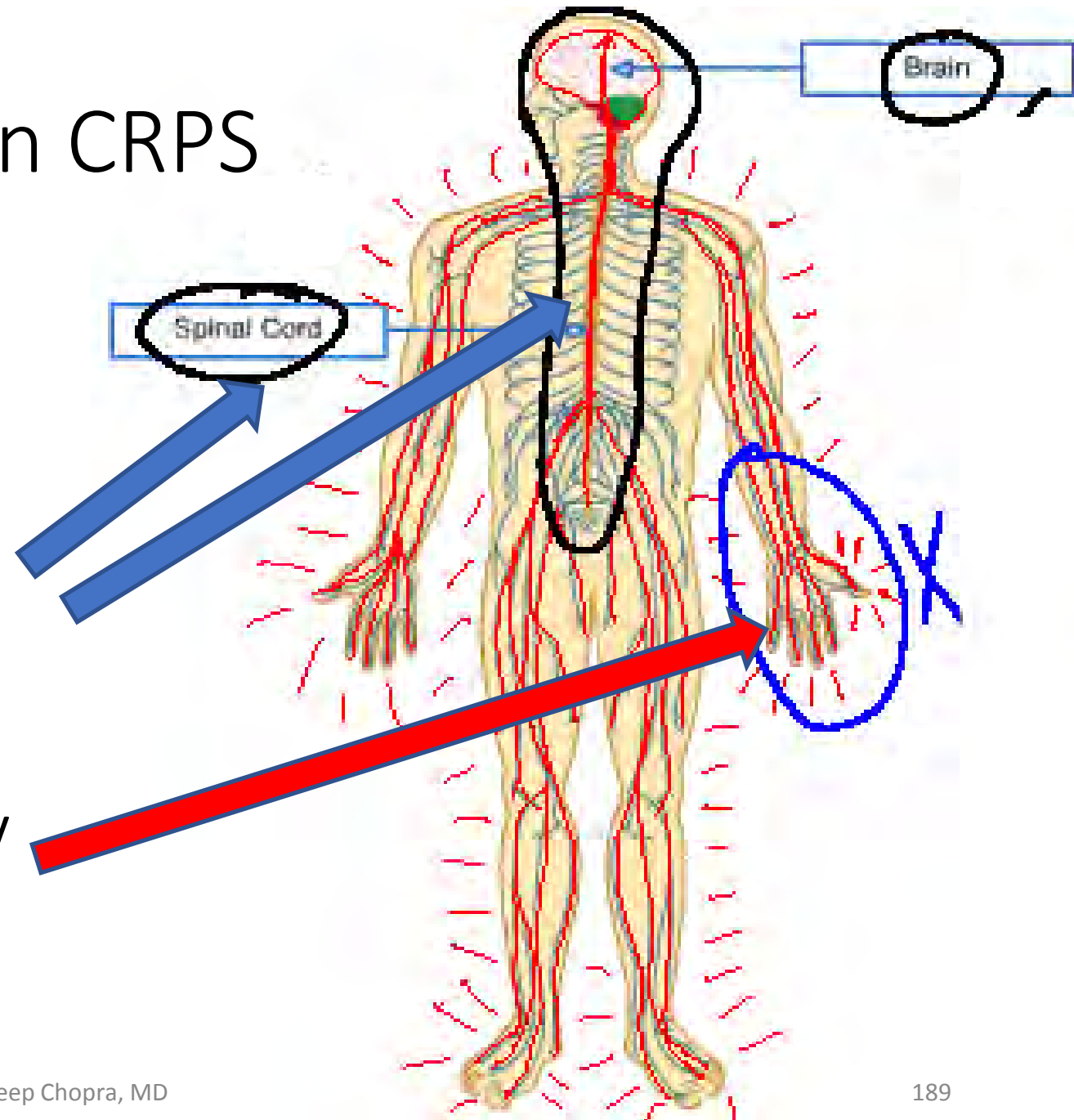
Central Sensitization

- The constant barrage of signals travelling up and down the brain and spinal cord makes the nervous system sensitive
- This is called Central Sensitization
- Hence, normal touch or a minor injury anywhere in the body, magnifies the pain greatly



Central Sensitization in CRPS

- In CRPS (and other chronic pains), the problem lies in the Central Nervous system
- Any treatment for CRPS, should be to treat it at the level of the Central Nervous system
- Treating the pain at the periphery may not help and may even make the pain worse



What really happens in CRPS /Central Sensitization

Central Sensitization

- Two things happen in Central Sensitization:
 1. Glial cells get activated
 2. NMDA receptors are activated

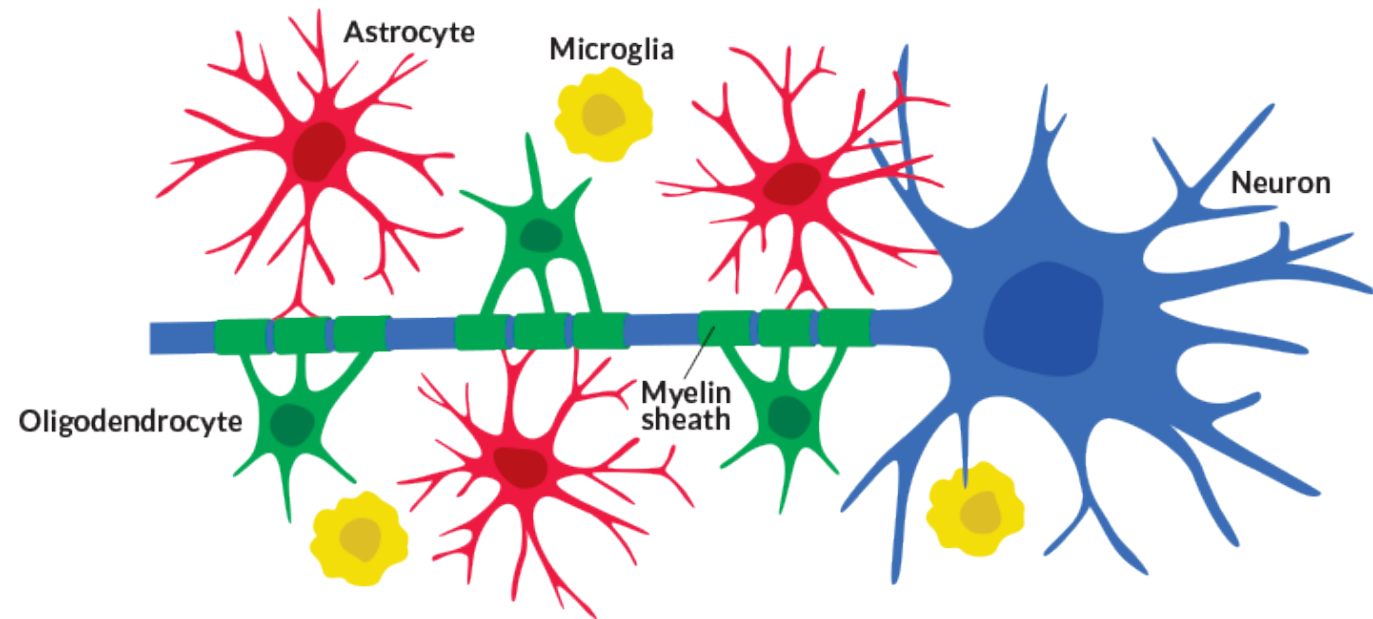
Central Sensitization: Activated Glial Cells

- Glial cells make up 70% of all the cells in our Central Nervous System
- Under normal circumstances, they remain dormant and are part of the nervous system's immune function

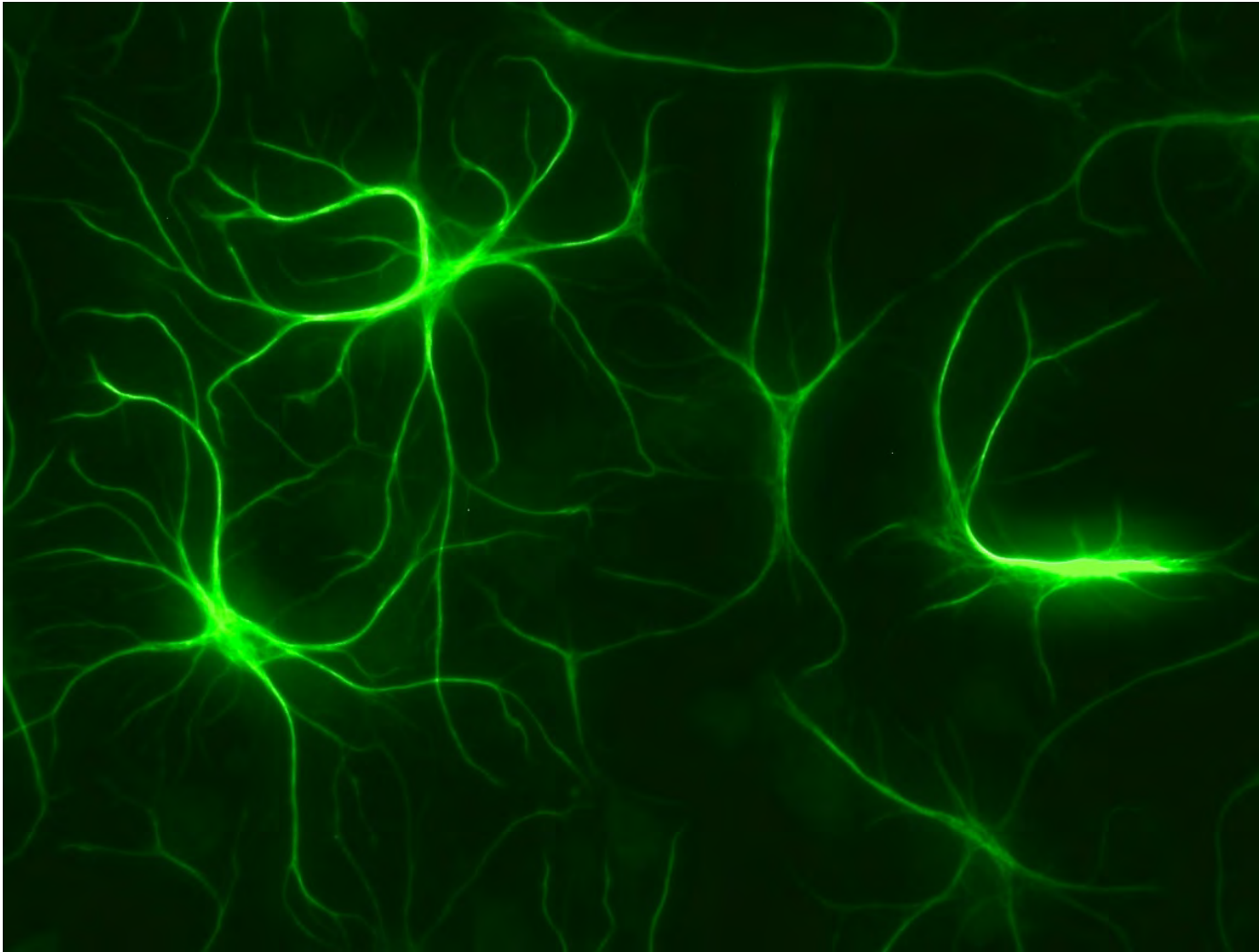
Milligan ED, Watkins LR (2009) Pathological and protective roles of glia in chronic pain. Nat Rev Neurosci 10:23–36

Central Sensitization: Activated Glial Cells

- Glial cells make up 70% of all the cells in our Central Nervous System
- Under normal circumstances, they remain dormant and are part of the nervous system's immune function



This is what glial cells look like



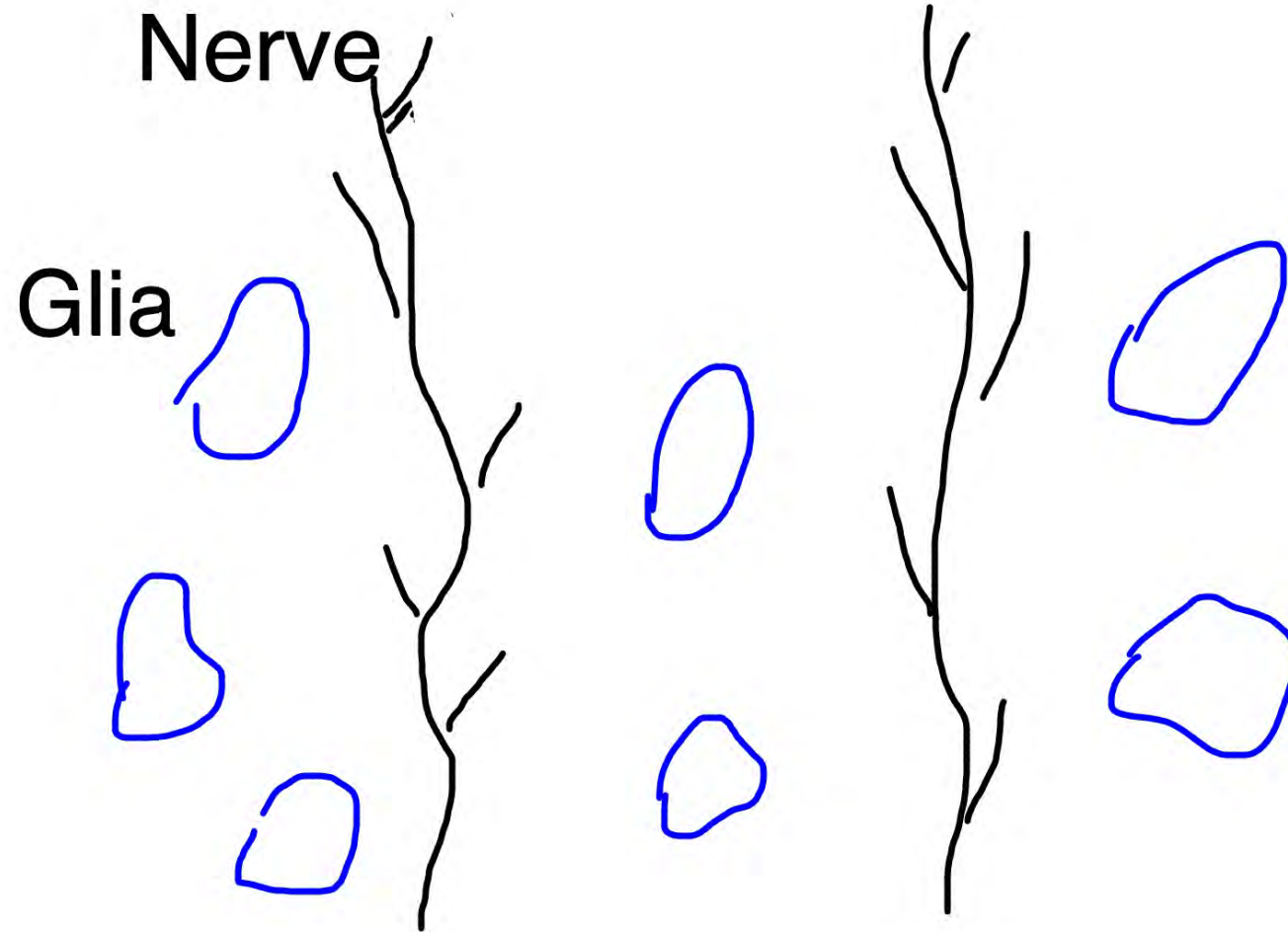
Courtesy Jarred Younger, PhD

Sonja Paetau, University of Helsinki

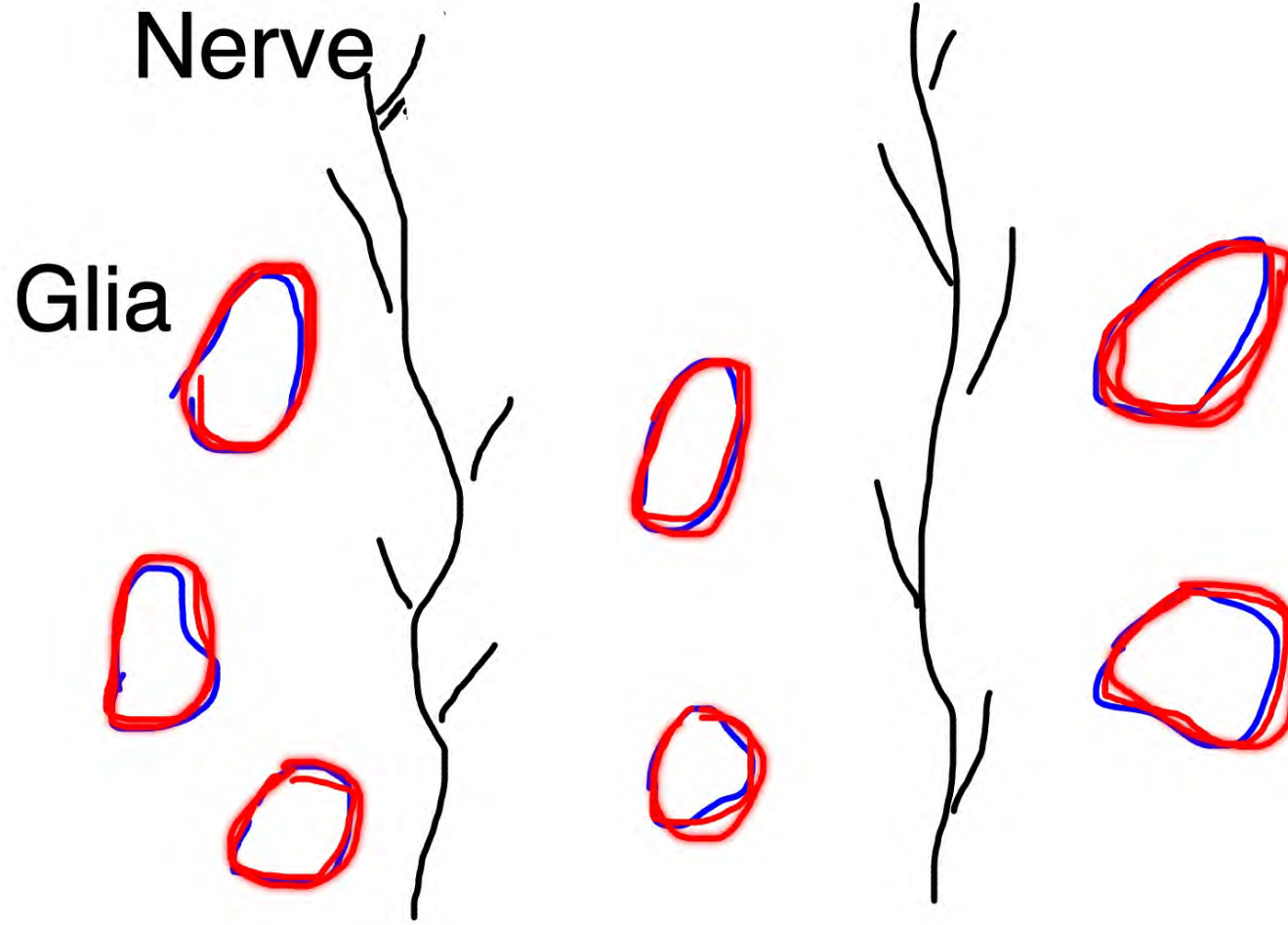
Central Sensitization: Activated Glial Cells

- In CRPS these glial cells are activated.
- Activated glia release certain chemicals (Cytokines) that cause nerves to become inflamed
- Glial cells are an important link between the nervous system and the immune system and inflammation and pain

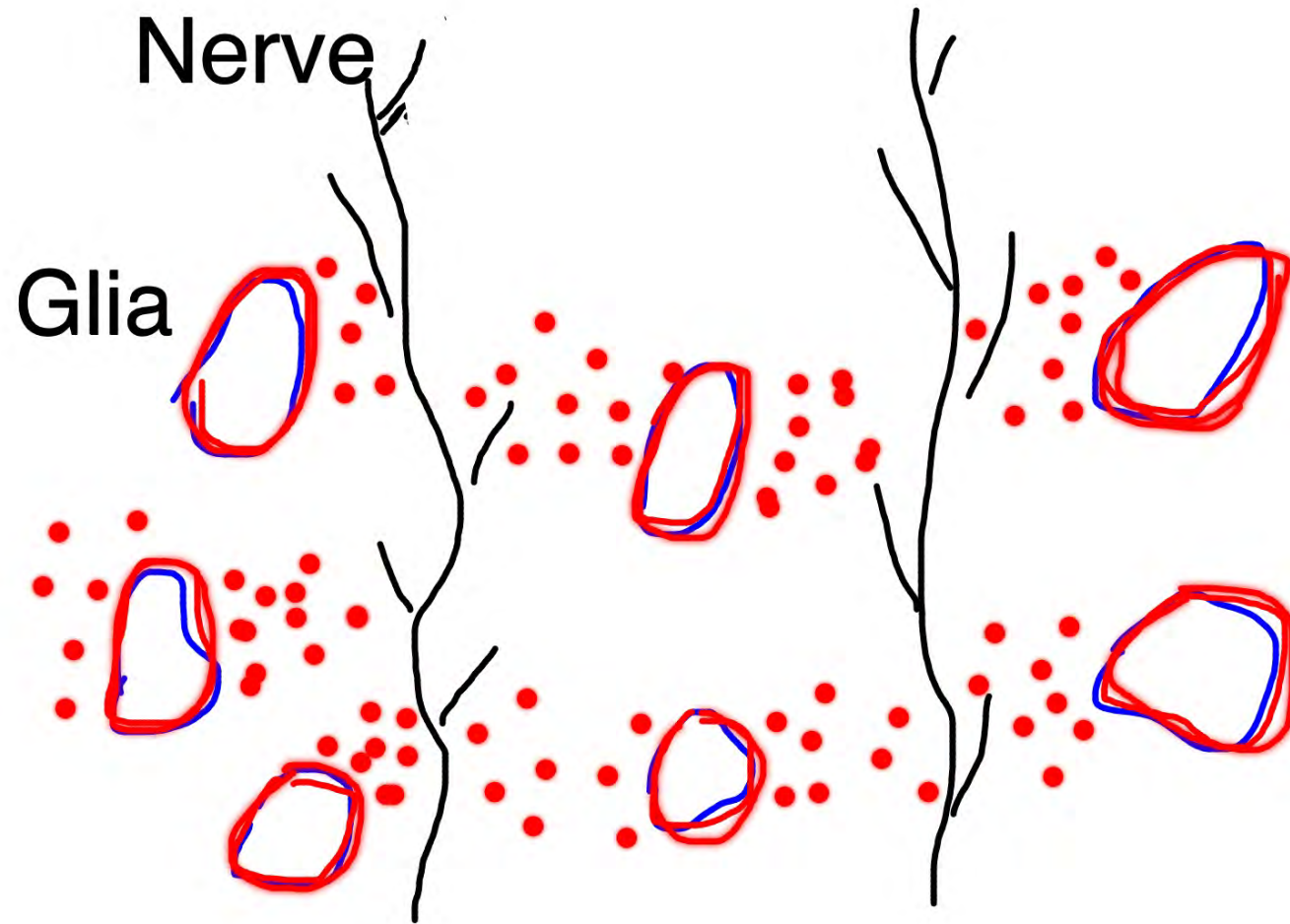
Glia and nerves under normal conditions



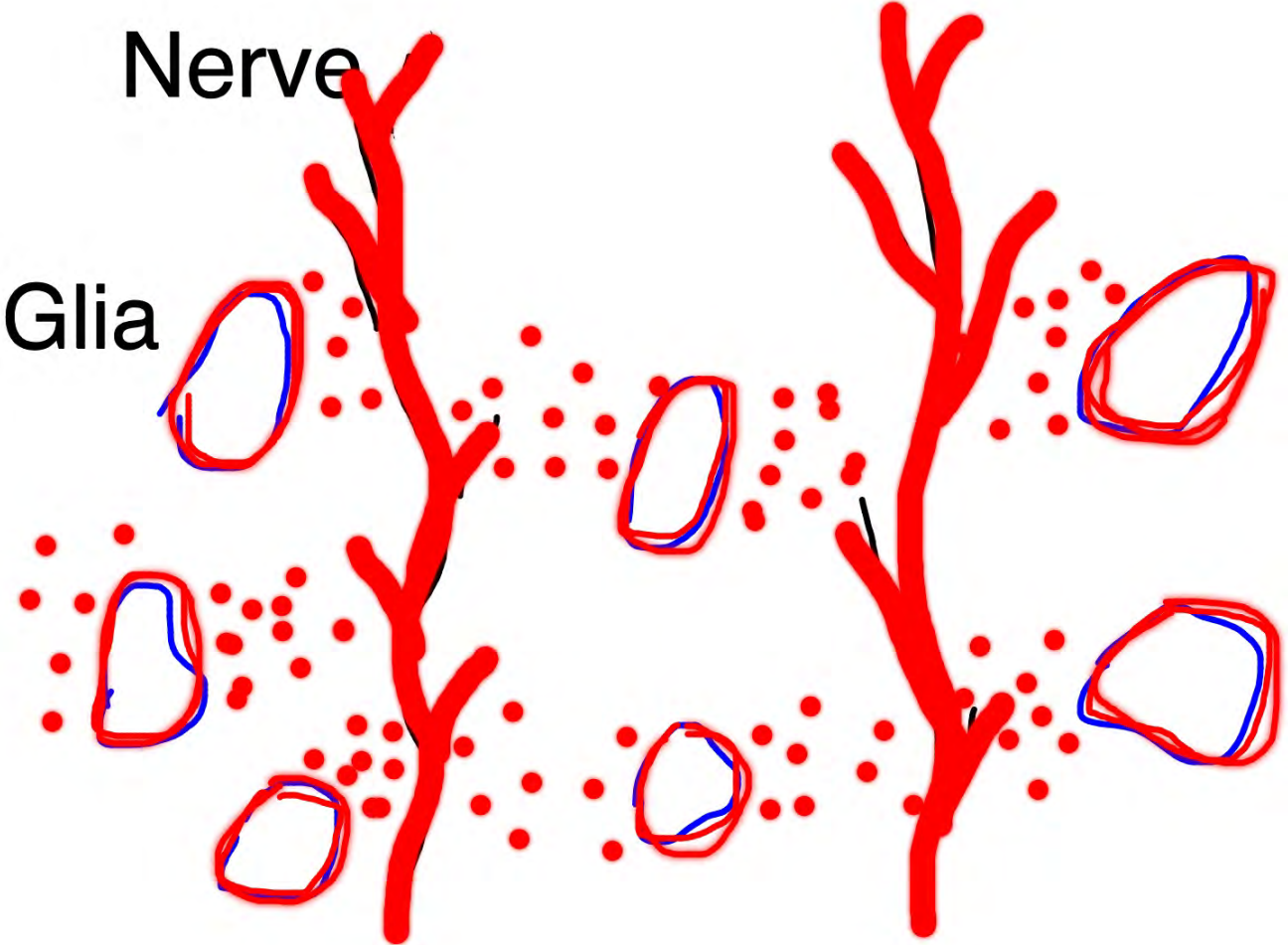
Activated Glia



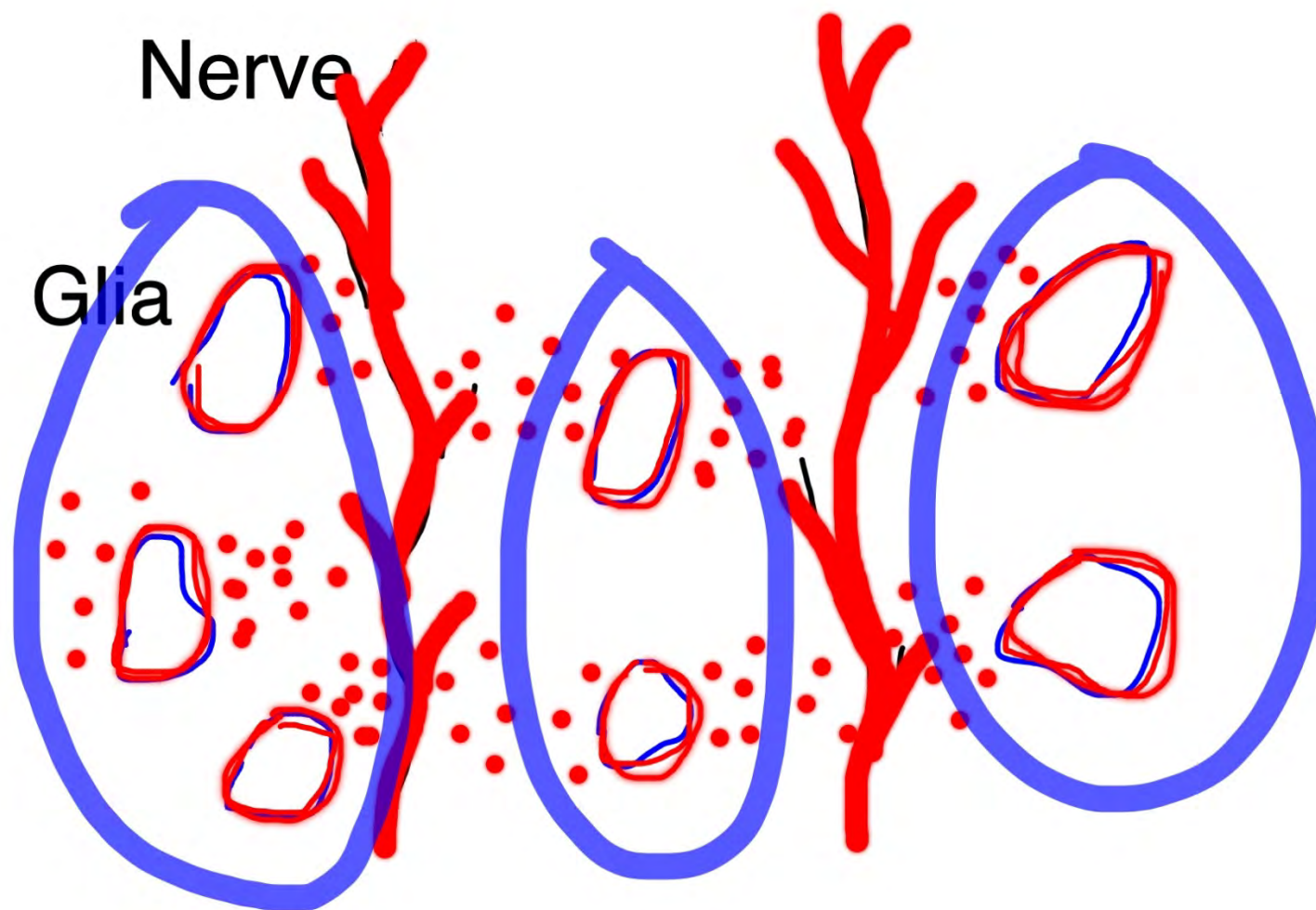
Chemicals released by activated Glia

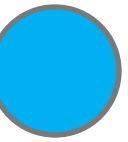


Nerve inflammation



The problem is with the glia cells





Spreading

- In long standing cases of CRPS, some patients develop similar symptoms in other areas of the body
- This is usually a result of increasing Central Sensitization.
- As the central nervous system become more and more sensitized, normal sensations to other parts of the body are felt as painful sensations.



- Management of Complex Regional Pain Syndrome should be directed towards what's causing the nerves to become inflamed and not just the nerves.
- Thus, it makes sense to treat the glial cell activation

Management

Complex Regional Pain Syndrome (CRPS)

Reflex Sympathetic Dystrophy (RSD)

Management of CRPS – step A

- The first step to do is to confirm if it is CRPS.
- Very often patients are told that it is CRPS because a cause of the pain could not be found

Management of CRPS – step B

- The next thing to do is to determine if its CRPS I or CRPS II

CRPS I and CRPS II

- In CRPS I – we do not know the exact nerve that is damaged
- In CRPS II – limited to a specific nerve distribution
- Some of the treatments are common to both
- In CRPS II, fixing the cause of the nerve damage may help

Management of CRPS – possible causes of CRPS I

- Unknown
- Autoimmune dysfunction
- Gastrointestinal (?)

CRPS II

This was the first CRPS discovered, even before CRPS I

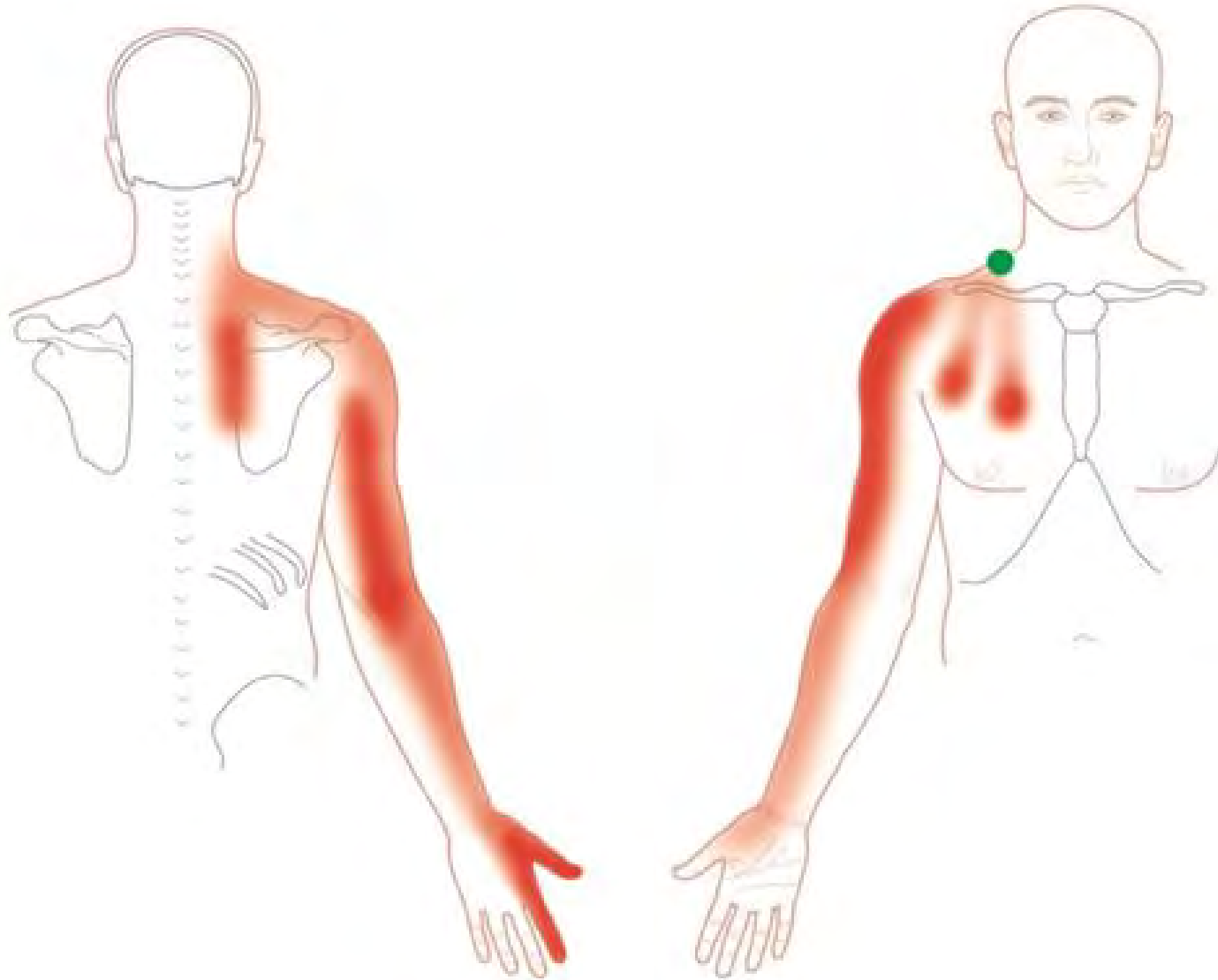
Management of CRPS – possible causes of CRPS II

- Upper extremity – Thoracic outlet syndrome, ulnar nerve entrapment
- Lower extremity – Common Peroneal neuralgia,
- Scarring after a nerve injury.
- Ehlers Danlos Syndrome – diffuse neuroinflammation from recurrent subluxations and dislocations.

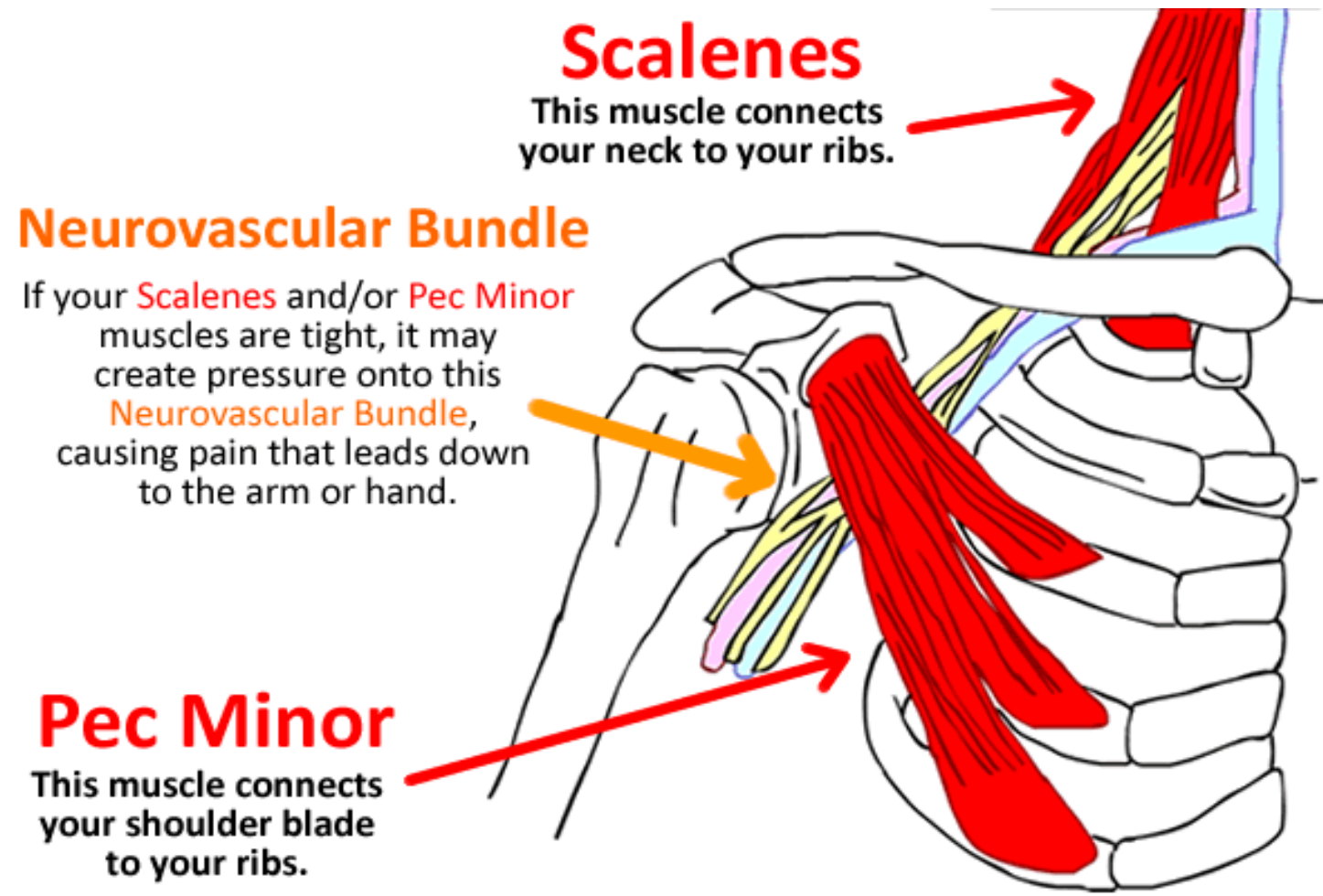
CRPS II

- Similar symptoms as CRPS I
- There is a major nerve damage that can be identified

Pain patterns in Thoracic Outlet syndrome



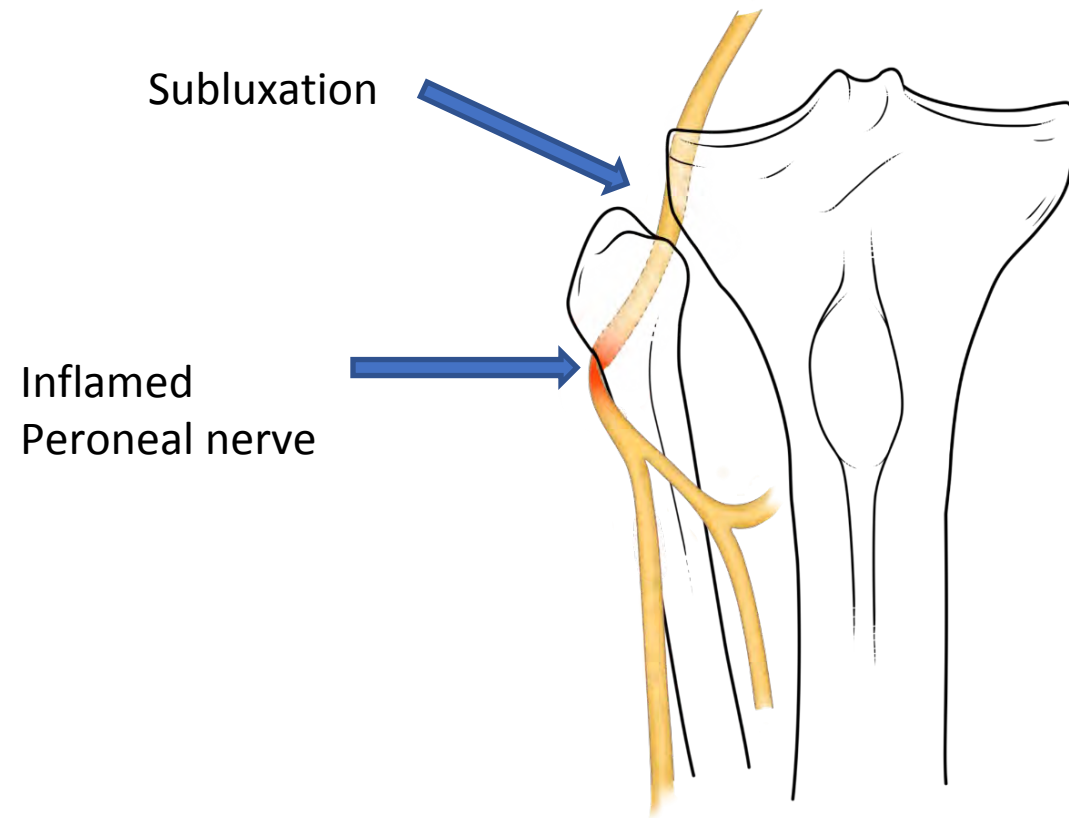
Thoracic Outlet Syndrome



CRPS II in the leg

- Symptoms of CRPS II may develop in the leg after impingement of the Common Peroneal nerve

Proximal Tibio-Fibular joint



Copyright Pradeep Chopra

CRPS II

- Treatment of CRPS II should be directed towards treating the cause of the nerve damage, for example:
- In Thoracic outlet syndrome the impingement of the nerves to the arm can be relieved by physiotherapy, Kinesio taping, Botox or even surgical correction
- Treatment of CRPS II in Ehlers Danlos Syndrome would be to stabilize the joints.

What really happens in CRPS



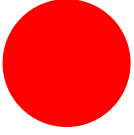
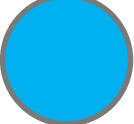
1. Inflammation of the nervous system
2. Sensitization of the structures in the body (skin, muscle, joints)
3. Vasomotor dysfunction: there is dysfunction of the nerves that control blood flow to the affected area (limbs with different temperatures). Chemicals (Norepinephrine) produced by these nerves increase pain
4. Maladaptive neuroplasticity: how the brain perceives the CRPS affected area. The brain tends to neglect the affected area. More about this in Graded Motor Imagery

Basic guidelines in treating CRPS

- Start treatment immediately, even if you suspect CRPS
- Must be evaluated by a physician who is very familiar with it, to start appropriate therapy
- Multidisciplinary approach - team work.

Start low, go slow

Grading of treatment

- Effective 
- Worth trying 
- Use caution 
- Scientific 



Commonly used medications

- Gabapentin
- Pregabalin (Lyrica™)
- Milnacipran (Savella™)
- Amitriptyline
- Duloxetine (Cymbalta™) - avoid



Other commonly used pain medications

- Acetaminophen / paracetamol
- Non steroidal anti-inflammatory drugs (NSAID) like ibuprofen, naproxen
- Steroids
- Not very helpful in CRPS. They may help a little when taken with other medications



Other commonly used pain medications

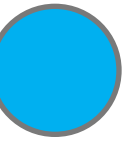
- Topical creams – useless and expensive
- Remember the pain is in the Central Nervous System (brain and spinal cord) not the limb



Ketamine

Central Sensitization

- Two things happen in Central Sensitization:
 1. Glial cells are activated
 2. NMDA receptors are activated



Central Sensitization - NMDA receptors

- In CRPS there is activation and proliferation of NMDA receptors
- Activation of the NMDA receptors makes the Central Nervous system more responsive to pain signals and decreases sensitivity to opioids

Milligan ED, Watkins LR (2009) Pathological and protective roles of glia in chronic pain. *Nat Rev Neurosci* 10:23–36



Ketamine

- Ketamine is a good NMDA Receptor blocker
- One of the safest anesthetic drugs
- Powerful analgesic even at low doses
- Poor absorption when administered orally.
- Effective as IV or sublingual (Troche) or nasal

Correll GE, Maleki J, Gracely EJ, Muir JJ, Harbut RE. Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. *Pain Medicine* 2004;5(3):263-75.

Factors that are important in getting the best out of a ketamine infusion



- Ketamine infusions are good only if done in conjunction with other therapies



Low dose Ketamine in CRPS

- Administered in sub-anesthetic doses – blocks NMDA receptors without causing too many side effects
- In CRPS it decreases Central Sensitization
- Rough estimates – 85% show improvement in daily activities, reduction in their medications and improved lifestyles
- It is not a cure. It is to be done along with other therapies

Correll GE, Maleki J, Gracely EJ, Muir JJ, Harbut RE. Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. *Pain Medicine* 2004;5(3):263-75.



Ketamine – out patient

- Increasing dose of ketamine over 10 days – loading dose
- Start at a low dose, increase everyday
- Infusion done over 4 to 5 hours
- Full standard monitoring
- Qualified personnel must be present at all times with the patient



IV Ketamine - boosters

- Very important part of the treatment protocol
- As the effect of the initial ketamine wears off, the glial cells begin to get activated again.
- Boosters for one day every 4 to 8 weeks depending on the severity, chronicity and response



Ketamine side effects

- Most of the side effects are temporary and short lived and reversible.
- We do not know of any long term side effects of ketamine infusions.
- Nausea, vomiting, colorful dreams, hallucinations, headache



Ketamine oral

- Oral ketamine – don't bother
- Unpredictable effects

Opioids

- Very little role in CRPS
- Opioids increase glial cell activation which increases central sensitization



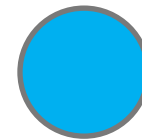
Low Dose Naltrexone

LDN



Low Dose Naltrexone (LDN)

- Competitive antagonist of opioid receptors
- Clinically used for 30 years for addiction
- Suppressive effects on the CNS glia, which....
- Attenuates production of pro-inflammatory cytokines and neurotoxic superoxides (chemicals that cause inflammation)



Low Dose Naltrexone (LDN)

- There are several theories as to how LDN may work.
 1. Transiently blocks opioid receptor leading to positive feedback production of endorphins (Zagnon)
 2. LDN increases production of OGF (opioid growth factor) as well as number of and density of OGF receptors by intermittently blocking the opiate receptor. Increased in OGF repairs tissue and healing.
 3. Naltrexone blocks the effect of TLR4 (Toll Like receptors) which decreases glial cell activation



Low Dose Naltrexone (LDN)

- Dose can vary anywhere between 1.75mg to 4.5mg
- May cause insomnia, mild headaches initially.
- Patients report increased physical activity, flare ups not as acute, better tolerance to pain.
- Recommend a trial of at least 6 months
- To avoid all opioids or tramadol.

Treatment of Complex Regional Pain Syndrome (CRPS) Using Low Dose Naltrexone (LDN)

Pradeep Chopra · Mark S. Cooper

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Abstract Complex Regional Pain Syndrome (CRPS) is a neuropathic pain syndrome, which involves glial activation and central sensitization in the central nervous system. Here, we describe positive outcomes of two CRPS patients, after they were treated with low-dose naltrexone (a glial attenuator), in combination with other CRPS therapies. Prominent CRPS symptoms remitted in these two patients, including dystonic spasms and fixed dystonia (respectively), following treatment with low-dose naltrexone (LDN). LDN, which is known to antagonize the Toll-like Receptor 4 pathway and attenuate activated microglia, was utilized in these patients after conventional CRPS pharmacotherapy failed to suppress their recalcitrant CRPS symptoms.

Keywords Chronic pain · Complex regional pain syndrome · CRPS · Reflex sympathetic dystrophy · RSD · Neuropathic pain · Naltrexone · Fixed dystonia · Allodynia · Vasomotor · Ulceration · Dystonic spasms · Conversion

dysfunctions. One of the characteristic symptoms of this condition is that the pain is out of proportion to the initial injury. Diagnoses of CRPS are often delayed because it is under recognized (Binkley 2012). If effective treatments are given early enough in progression of the disease, there is reduced chance for the spread of regional pain, autonomic dysfunction, motor changes, and negative sensory symptoms, such as hypoalgesia (Marinus et al. 2011). As CRPS progresses, it becomes refractory to sympathetic nerve blocks, conventional analgesics, anticonvulsants and antidepressants.

During neuroimmune activation, TLR4 (Toll-Like Receptor 4) is upregulated in microglia, resident immune cells of the central nervous system (Watkins et al. 2009). After transection of the L5 spinal nerve in the rat, TLR4 expression is increased in spinal microglia. This correlates with the rodent developing neuropathic pain (Tanga et al. 2005). From a post-mortem analysis of a CRPS patient, activated microglia and

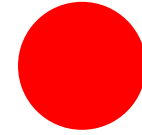
Low Dose Naltrexone (LDN) in Germany

- <http://www.ldn4ms.de>
- This website has more information on LDN



Sensory Deprivation Therapy

- Isolation tank.
- Warm water with high quantities of EPSOM salt
- Subject floats on the water because of the high salt content
- No lights or sounds in the room
- All external stimulation to the Central Nervous system (brain and spinal cord) is cut off.

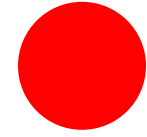


Sympathetic Nerve blocks

- Stellate ganglion blocks for upper extremity
- Lumbar sympathetic blocks for lower extremity
- No good data on long term efficacy of these blocks
- Very risky procedures
- No diagnostic or therapeutic value
- Temporary at best

Price DD, Long S, Wilsey B, Rafii A. Analysis of peak magnitude and duration of analgesia produced by local anesthetics injected into sympathetic ganglia of complex regional pain syndrome patients. *Clin J Pain* 1998;14(3):216-26.

Azad SC, Beyer A, Romer AW, Galle-Rod A, Peter K, Schops P. Continuous axillary brachial plexus analgesia with low dose morphine in patients with complex regional pain syndromes. *Eur J Anaesthesiol* 2000;17(3):185-8.



Electrical stimulation

- Different therapies (Scrambler etc) available that involve electrical stimulation of nerves.
- Very unhelpful
- Stimulating nerves in CRPS is not a good idea
- May try a TENS unit

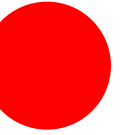


Spinal Cord Stimulator (SCS)

- An electrode is inserted surgically into the epidural space and connected to an implanted generator
- The electrode produces an electrical current is felt as a tingling sensation and suppresses pain.
- Mechanism of action unknown
- Painful and expensive
- No great benefit after a few years
- Dorsal root ganglion stimulator - new

Kemler MA, Barendse GA, Kleef M van, Vet HC de, Rijks CP, Furnee CA, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med* 2000;343(9):618-24.

Bennett DS, Alo KM, Oakley J, Feler CA. Spinal cord stimulation for complex regional pain syndrome I (RSD): a retrospective multicenter experience from 1995 to 1998 of 101 patients. *Neuromodulation* 1999;2:202-10.



Spinal Cord Stimulator (SCS)

- 25% to 50% of patients develop complications requiring further surgery.
- In a huge study SCS reduced pain and improved quality of life but did not improve function for up to 2 years after implantation.
- From 3 years after implantation there was no difference between those who had it implanted and those who did not

Kemler MA, Barendse GA, Kleef M van, Wildenberg FA van den, Weber WE. Electrical spinal cord stimulation in reflex sympathetic dystrophy: retrospective analysis of 23 patients. *J Neurosurg* 1999;90(1 suppl):79-83.

Calvillo O, Racz G, Didie J, Smith K. Neuroaugmentation in the treatment of complex regional pain syndrome of the upper extremity. *Acta Orthop Belg* 1998;64(1):57-63.

Kemler MA, Vet HC de, Barendse GA, Wildenberg FA van den, Kleef M van. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. *Ann Neurol* 2004;55(1):13-8.

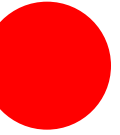


Physical therapy modalities



Physical movement

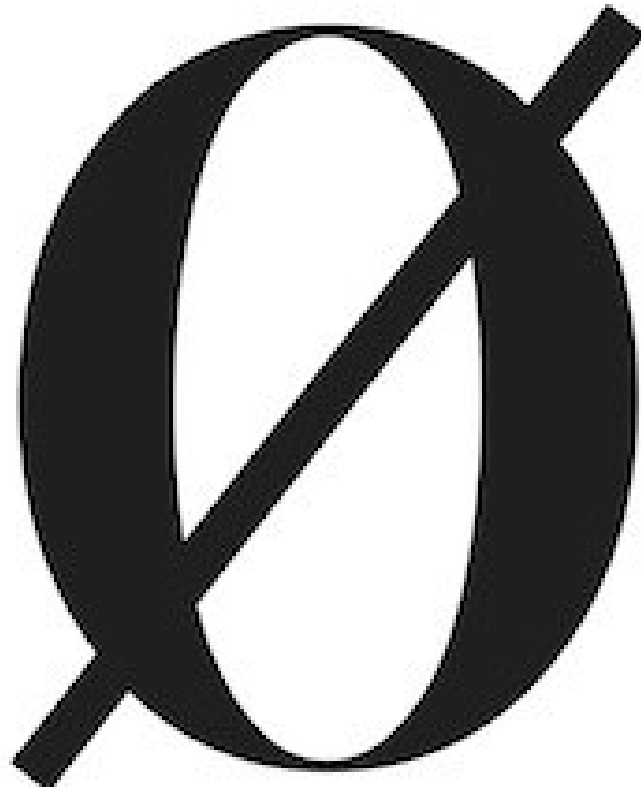
- Moving the limbs as much as possible is very important to prevent atrophy and contractures
- Physiotherapy does not have to be hard and difficult.
- It should be slow and paced.
- Its more important to be consistent every day.
- "No pain, no gain" – does not apply here



Desensitization

- Desensitization exercises have been recommended for a long time for CRPS
- Rice bowl, rubbing with a piece of cloth, paraffin bath, etc.
- Worsens Central Sensitization

Literature to support desensitization in CRPS





Graded Motor Imagery

Stage 1: Left/Right discrimination – Graded Motor Imagery



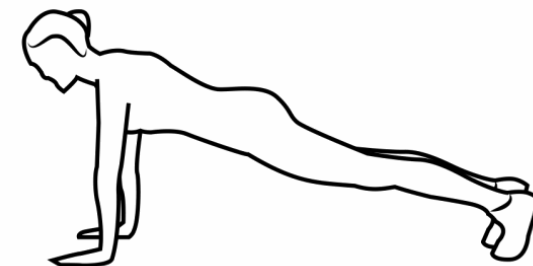
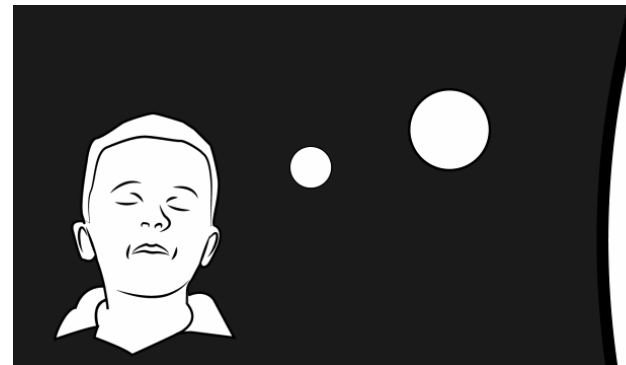
- In CRPS, people often lose the ability to identify left or right images of their painful body parts.
- This ability is important for normal recovery from pain
- The good news is that the brain is plastic and changeable.
- The ‘Recognise’ app helps regain this ability

Stage 2: Explicit Motor Imagery - Graded Motor Imagery



- The process of thinking about moving without actually moving
- Imagined movement can actually be hard work if you are in pain.
- 25% of our brain is made of 'mirror neurons' – they start firing when you think of moving or even watch someone else move
- Imagining movements before actually moving you use the same neurons that you would use when you actually move

www.gradedmotorimagery.com
Neuro Orthopedic group, Australia

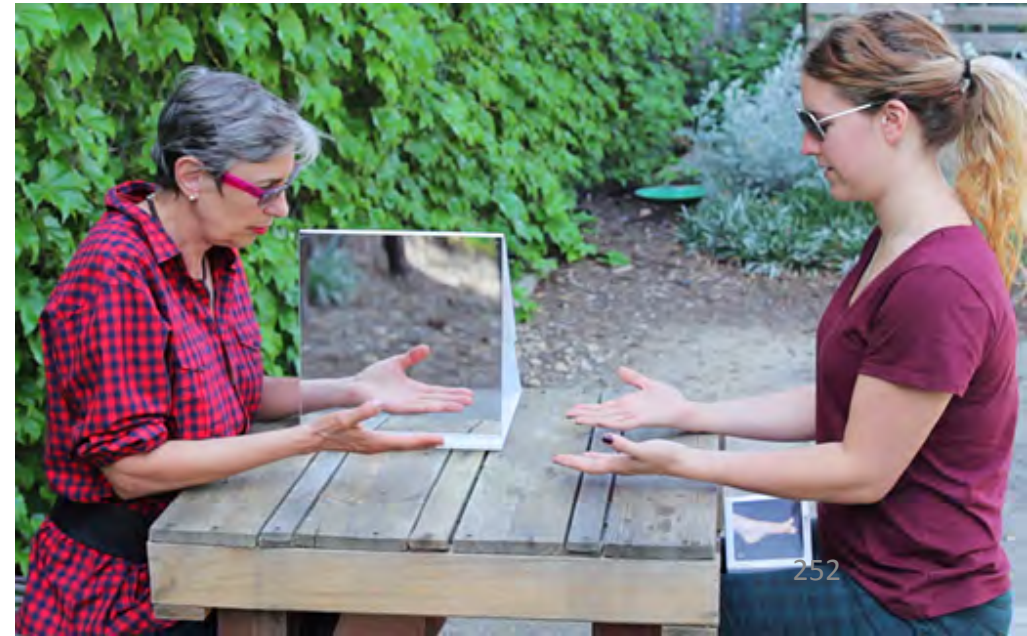




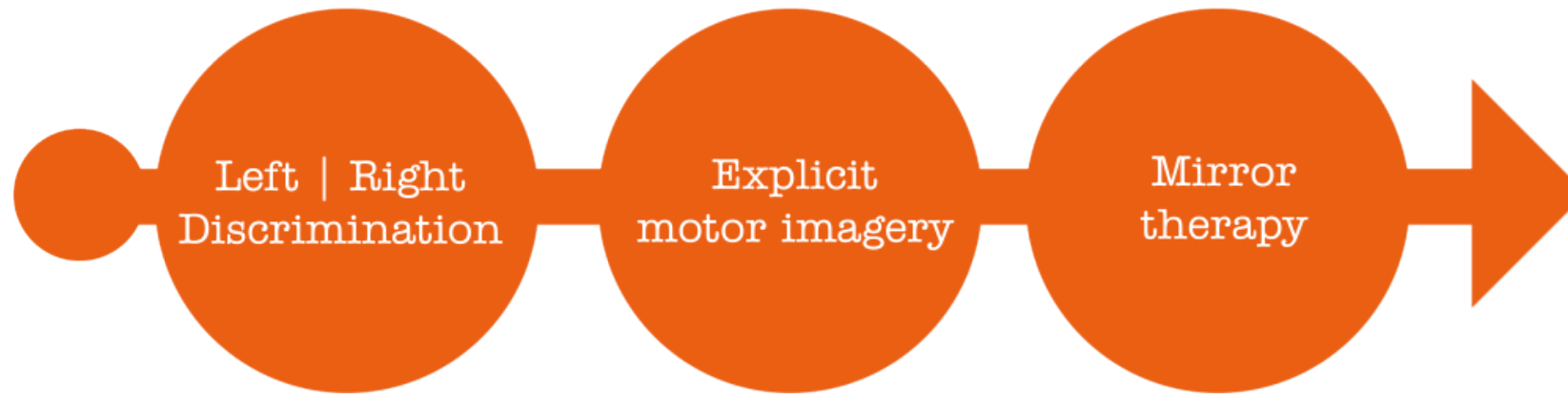
Stage 3: Mirror therapy- Graded Motor Imagery

- By hiding the affected limb behind a mirror, you can trick the brain into believing that the reflection of the normal hand is the affected limb.
- In your brain you are exercising the affected limb as you move the normal limb.

www.gradedmotorimagery.com
Neuro Orthopedic group, Australia



Three stages of Graded Motor Imagery delivered sequentially



- Left / right discrimination
- Explicit Motor imagery
- Mirror therapy
- www.gradedmotorimagery.com

Gastrointestinal system and CRPS

How our foods may affect our pain

Gastrointestinal system (GI system) and CRPS

- In CRPS the diversity of bacteria is less (normally, approximately 1000 different types of bacteria)
- This causes GI inflammation, the lining of the intestines is damaged, and increased production of pro-inflammatory cytokines
- TLR4 receptor activity is increased. This has been associated with inflammation.
- TLR4 is one of the receptors where LDN works.

Erin R. Reichenberger a, Guillermo M. Alexander b, Marielle J. Perreault b, Jacob A. Russell c, Robert J. Schwartzman b, Uri Hershberg a,1, Gail Rosen. Establishing a relationship between bacteria in the human gut and Complex Regional Pain Syndrome. *Brain, Behavior, and Immunity* 29 (2013) 62–69

Gastrointestinal system (GI system) and CRPS

- Are we destroying our 'friendly' bacteria with our artificial foods, preservatives, chemicals, antibiotics?
- SIBO – Small Intestine Bacterial Overgrowth – talk to Gastroenterologist
- We need more research in to this

Identification and Treatment of New Inflammatory Triggers for Complex Regional Pain Syndrome: Small Intestinal Bacterial Overgrowth and Obstructive Sleep Apnea

Leonard B. Weinstock, MD, FACG,*†‡ Trisha L. Myers, PA-C,‡ Arthur S. Walters, MD,§ Oscar A. Schwartz, MD,*|| Jarred W. Younger, PhD,¶#** Pradeep J. Chopra, MD,††‡‡ and Anthony H. Guarino, MD‡‡

Complex regional pain syndrome (CRPS) is evoked by conditions that may be associated with local and/or systemic inflammation. We present a case of long-standing CRPS in a patient with Ehlers-Danlos syndrome in which prolonged remission was attained by directing therapy toward concomitant small intestinal bacterial overgrowth, obstructive sleep apnea, and potential increased microglia activity. We theorize that cytokine production produced by small intestinal bacterial overgrowth and obstructive sleep apnea may act as stimuli for ongoing CRPS symptoms. CRPS may also benefit from the properties of low-dose naltrexone that blocks microglia Toll-like receptors and induces production of endorphins that regulate and reduce inflammation. (A&A Case Reports. 2015;XXX:00–00.)

Complex regional pain syndrome (CRPS), formally known as reflex sympathetic dystrophy, is a neuropathic pain disorder that may fail to respond to current therapy including a variety of medications, nerve blocks, and ketamine infusions.^{1,2} The incidence of CRPS is uncertain because there are few epidemiological studies. In a Mayo Clinic study, the rate was 5.46 per 100,000 person-years compared with a 6-fold larger study in the Netherlands where the rate was 26.2 per 100,000 person-years.^{3,4} A marked female predominance was noted in each study. A familial occurrence of CRPS has been described.⁵ The natural history of CRPS varies widely. The Mayo Clinic reported that 56 of the 74 patients with CRPS for 1 month to 5 years had complete remission after various treatments. Spontaneous remission was observed when the initial symptoms were mild.³ By way of comparison, there were no remissions in 656 Drexel University patients who had CRPS for 1 to 46 years.⁶ Pain had only modest improvement with their treatments. No spontaneous remissions occurred in 102

Dutch database patients who had CRPS for 2.1 to 10.8 years.⁷ Progressive disease was reported in 16%, and permanent disability was present in 31% of the Dutch patients.

Pathophysiologic consequences of cytokine release, microglia activation, central sensitization, and autonomic nervous system dysfunction result in regional pain along with vasomotor, motor/trophic, and sudomotor/edema dysfunction.^{1,2,8,9} Microglia cells are an integral part of the anatomic framework of the nervous system with attachments to astrocytes.¹⁰ They act as neuromodulators, which alter central nervous cell and spinal sensory neuron excitability. Various syndromes marked by hyperalgesia including fibromyalgia and CRPS may be mediated by microglia cell activation as a consequence of proinflammatory cytokines.^{11,12} Events known to trigger the onset of CRPS include bone fractures, sprains, trauma (injections, nerve injury, surgery, burns, and frostbite), nerve injury, infection, pregnancy, myocardial infarction, and stroke.¹² Some of these triggers may be associated with local and/or systemic inflammation.^{13–17} In stroke-associated CRPS, inflammation from the stroke has been theorized as one of several possible pathophysiologic mechanisms.¹⁷

In light of the complex pathophysiology of CRPS and that no single therapy is completely effective, it is desirable

From the Departments of *Anesthesia and †Internal Medicine, Washington University School of Medicine, St. Louis, Missouri; ‡Specialists in Gastroenterology, LLC, St. Louis, Missouri; §Department of Neurology, Vanderbilt University, Nashville, Tennessee; ||Sleep and EEG Laboratory, Barnes Jewish West County, BJC Medical Group Center for Sleep Medicine, St. Louis,

Future

- Adenosine A3 agonists – in phase II and III trials for psoriasis, rheumatoid arthritis)
- Subcutaneous Ketamine for acute phase
- Tadalafil (Cialis)
- Tocilizumab (Acetemra TM) – recombinant anti-human IL-6 receptor antibody
- Thalidomide – suppresses TNF-alpha. 31% response in CRPS



Bisphosphonates

Class of drugs used to treat bone loss.

Bisphosphonates

- Commonly used to treat osteoporosis (bone loss)
- Osteoblasts – cells that build bone. They use vitamin D
- Osteoclasts – break down bone
- Bisphosphonates destroy osteoclasts thus helping osteoblasts do their job of making bone

Bisphosphonates

- Osteoblasts (bone building cells) Vitamin D to function
- It seems like improving healthy bone development either by improving osteoblasts functioning or by destroying osteoclasts (bone destroying cells) helps CRPS



Bisphosphonates

- Clodronate (300mg) daily IV for 10 days – pain, swelling, movement range in acute CRPS
- Alendronate (7.5mg) once IV - pain, swelling, movement range in acute CRPS
- Pamidronate 60mg IV
- Use in long standing cases

Forouzanfar T, Koke AJ, Kleef M van, Weber WE. Treatment of complex regional pain syndrome type I. Eur J Pain 2002;6(2):105-22.

Adami S, Fossaluzza V, Gatti D, Fracassi E, Braga V. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. Ann Rheum Dis 1997;56(3):201-4.

Neridronate

- Very similar to alendronate (Fosamax[®]), Pamidronate (Aredia[®])
- Very small trial.
- Very select group of patients.
- Only patients who had bone changes were studied.
- Better studies being done which are more realistic

Varenna M, Adami S, Rossini M. Treatment of CRPS I with neridronate: a randomized, double blind, placebo controlled study. *Rheumatology*.
Doi 110.1093/rheumatology/kes312 274,299



Vitamin D

- Vitamin D promotes Calcium absorption in the gut
- Helps bone development
- Helps muscle and immune function
- Reduces inflammation

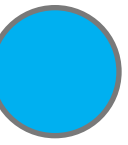


Vitamin D

- Rather than seek treatments with bisphosphonates, work towards improving vitamin D levels first
- Really very important to check and make sure that vitamin D levels are adequate



FREE RADICAL SCAVENGERS



Free Radicals – what are they?

- Human body is made up of cells
- Cells are made up of atoms
- Atoms are made up of electrons and protons (1:1)

Free radicals

- The increased sympathetic nerve activity in the area cause blood vessels to constrict, hence the cold, pale limb.
- Reduced blood flow, tissue damage and increased acid production
- This causes increased production of free radicals which increase pain in the area.

Free Radicals – what are they?

- When tissues break up, some electrons are left free to float around.
- These unbalanced molecules are called free radicals
- These unbalanced molecules become very unstable and attack another molecule or electron to grab onto for stability.
- In our body, when these unstable electrons attack other molecules to achieve stability they damage human cells – nerves, muscles

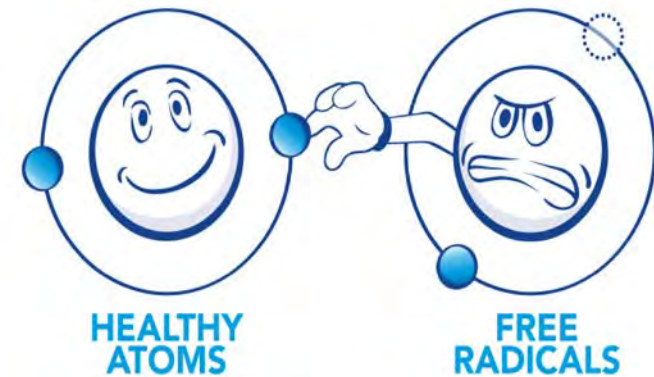
Free Radicals

- Our body is made up of healthy, balanced atoms.
- Because of chemical processes on our body, the atoms lose an electron
- When they lose an electron, they become unbalanced – called Free Radicals.



Free Radicals

- Free radicals stabilize themselves by stealing an electron from healthy tissue
- When they steal an electron, they damage healthy tissue and produce more free radicals



Free Radicals

- Antioxidants, also known as Free Radical Scavengers donate an electron to the Free Radicals





Free Radical scavengers (Antioxidants)

- Alpha Lipoic Acid
 - Vitamin C
 - DMSO (Dimethyl sulphoxide)
 - N-Acetyl Cysteine (NAC)
-
- They are available over the counter



Alpha Lipoic acid (ALA) 1

- Free Radical scavenger
- Promising results in diabetic neuropathy and other polyneuropathies
- No trials in CRPS
- Has been approved in Germany for treating neuropathic pain



Alpha Lipoic acid (ALA)

- Its also helps with autonomic neuropathy (common in CRPS) POTS
- Effective when taken as IV (Intravenous)
- May be taken orally
- Dose: 600mg to 1200mg per day
- Start low, go slow



Vitamin C

- Natural antioxidant
- There are several studies that have shown that Vitamin C can prevent CRPS after a fracture
- Vitamin C 500 mg was shown to prevent development of CRPS
- Vitamin C 500mg/day may help in patients who have developed CRPS
- No value to going higher than 500mg / day

Zollinger Paul, Tuinebereijer, Keir R, Breederveld, 1999, Lancet
Jae Hun Kim¹, Yong Chul Kim² *International Journal of Medical Sciences*
2017; 14(1): 97-101. doi: 10.7150/ijms.17681



DMSO 50% - Dimethyl Sulphoxide

- Topical use only.
- Particularly helpful for 'warm' CRPS
- CRPS less than 1 year - three month course of DMSO applied 5 times topically every day
- CRPS more than 1 year – One month trial course of DMSO everyday.
- If trial helps, then continue

Geertzen JH, Bruijn H de, Bruijn-Kofman AT, Arendzen JH. Reflex sympathetic dystrophy: early treatment and psychological aspects. Arch Phys Med Rehabil 1994;75(4):442-6.

Zuurmond WW, Langendijk PN, Bezemer PD, Brink HE, Lange JJ de, Loenen AC van. Treatment of acute reflex sympathetic dystrophy with DMSO 50% in a fatty cream. Acta Anaesthesiol Scand 1996;40(3):364-7.



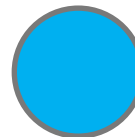
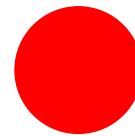
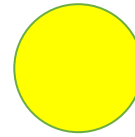
N- Acetyl Cysteine (NAC)

- Useful for cold allodynia
- N-Acetylcysteine 600mg three times a day for three months
- Start low, go slow

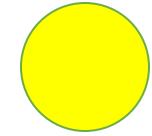
Perez RS, Zuurmond WW, Bezemer PD, Kuik DJ, Loenen AC van, Lange JJ de, et al. The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study. *Pain* 2003;102(3):297-307

Grading of treatment

- Effective
- Worth trying
- Use caution
- Nerdy stuff



Oxytocin

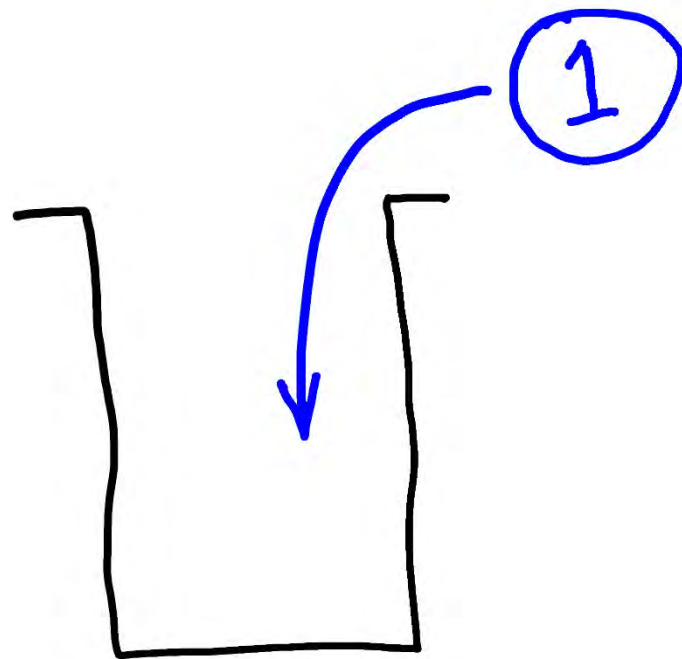


- Chemical produced naturally in the brain
- Taken as a nasal spray, sublingual
- Especially helpful in flare ups (acute pain)
- Two mechanisms by which oxytocin reduces pain
 - Directly on the spinal cord to turn down pain signals
 - By releasing endorphins (morphine produced by the body).

NC10 rule

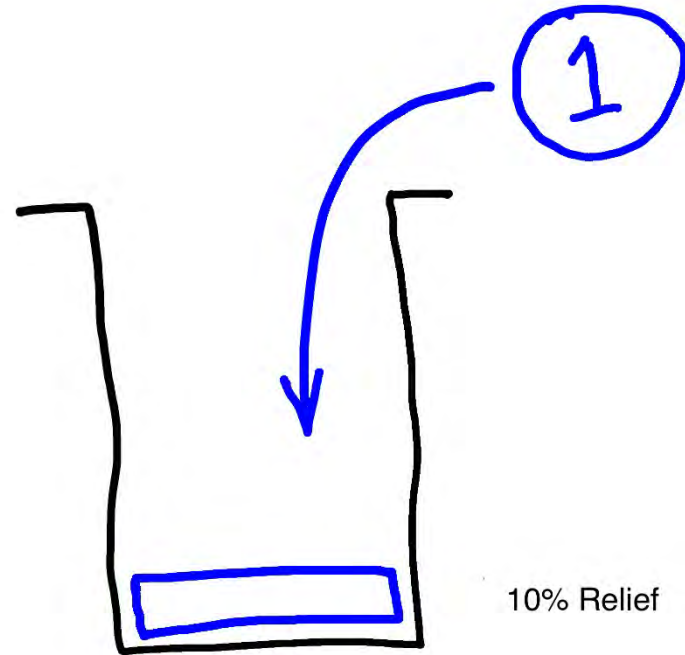
Expectations from different therapies

NC 10 rule



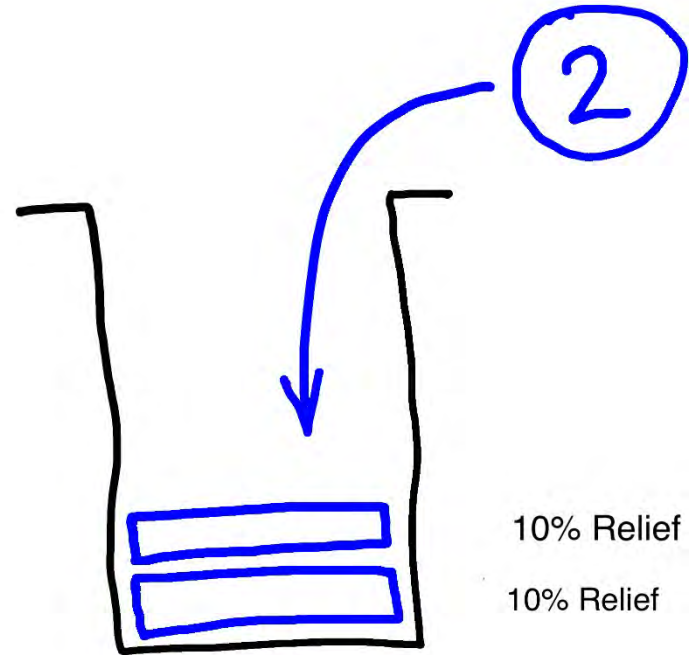
NC 10 rule

NC10 rule



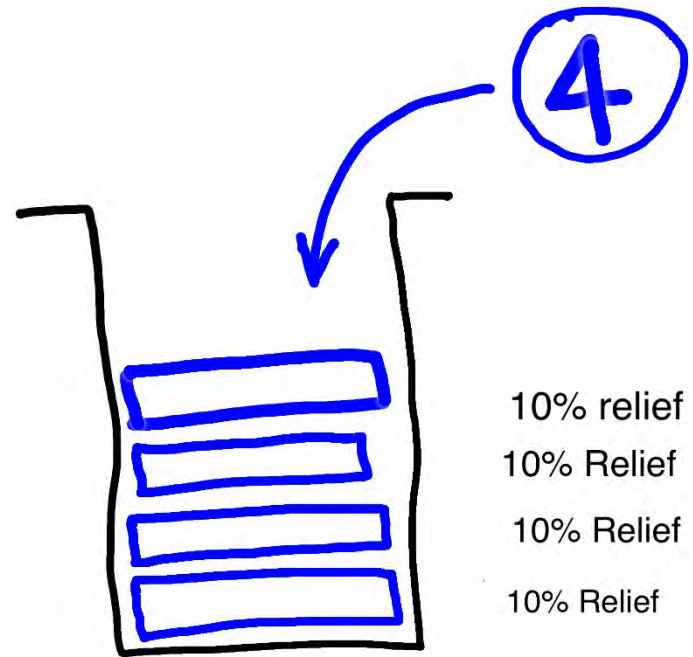
NC 10 rule

NC10 rule



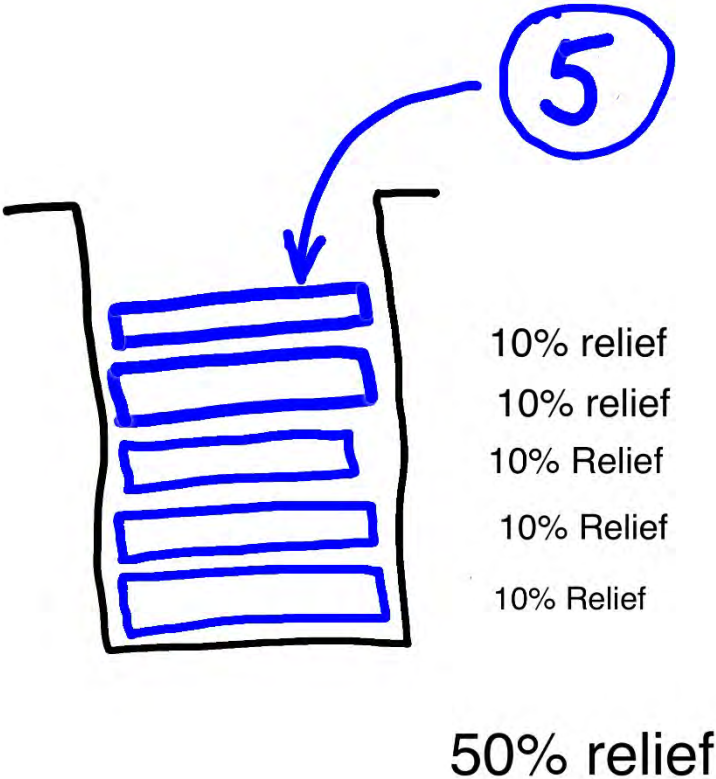
NC 10 rule

NC10 rule



NC 10 rule

NC10 rule



Pain receptor behavior

- When we take a drug for pain for a long time there is downregulation of the receptors, which means....
- The body's response to the drug is not as good.
- If we stop the drug for sometime, the receptors are upregulated, which means....
- Restarting the drug gets a better response at a lower dose.

Pain receptor behavior - drug rotation

- Ideally, a person could switch between drugs of a different class.
- For example, a patient on opioids for some months can take a 'drug holiday' for a few weeks to months.
- During this time, they can try medicinal marijuana (if legal) or ketamine (sublingual) or NSAID's
- After some time restart opioids at a lower dose.



Hyperbaric Oxygen

- No good evidence that it helps in the long term
- Anecdotal reports (mostly from hyperbaric centers)
- Different types – high pressure and low pressure
- Waste of time and money

[Kiralp MZ, Yildiz S, Vural D, Keskin I, Ay H, Dursun H. J Int Med Res. 2004 May-Jun;32\(3\):258-62. Effectiveness of hyperbaric oxygen therapy in the treatment of complex regional pain syndrome](#)

Physical therapy modalities

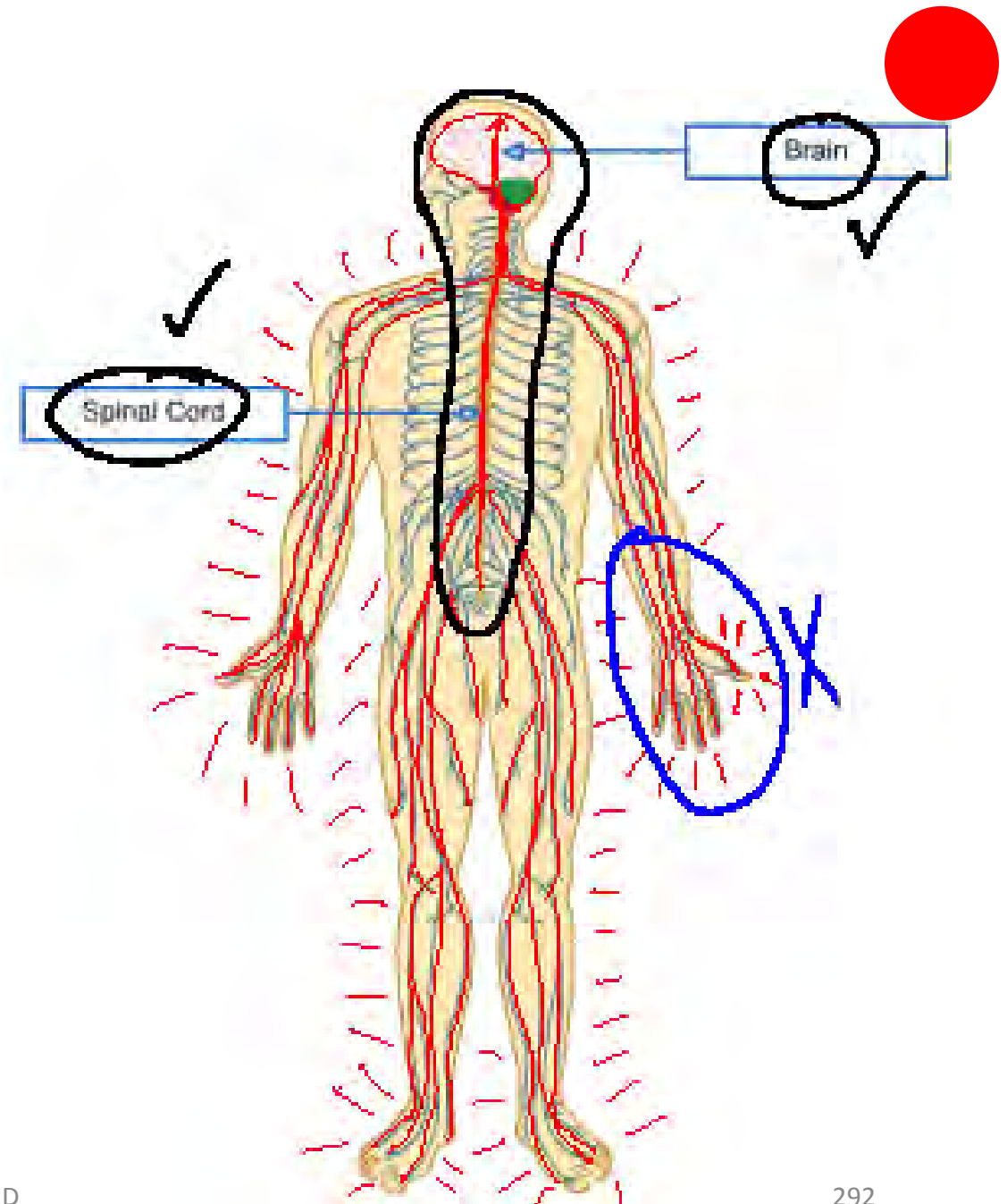


Physical movement

- Moving the limbs as much as possible is very important to prevent atrophy and contractures
- Physiotherapy does not have to be hard and difficult.
- It should be slow and paced.
- Its more important to be consistent every day.
- "No pain, no gain" – nonsense

Avoid desensitization

- The source of the pain is in the brain and spinal cord.
- Repetitive rubbing of the painful limb will only worsen Central Sensitization



Palmitoyl ethanol amide (PEA)

PEA

- Palmitoylethanolamide (PEA) or Palmidrol
- Nobel Prize winner Prof. Rita Levi-Montalcini
- Endogenous lipid
- Very good studies to show its usefulness in managing neuropathic pain
- Available as PeaPure, Normast, Pelvilen

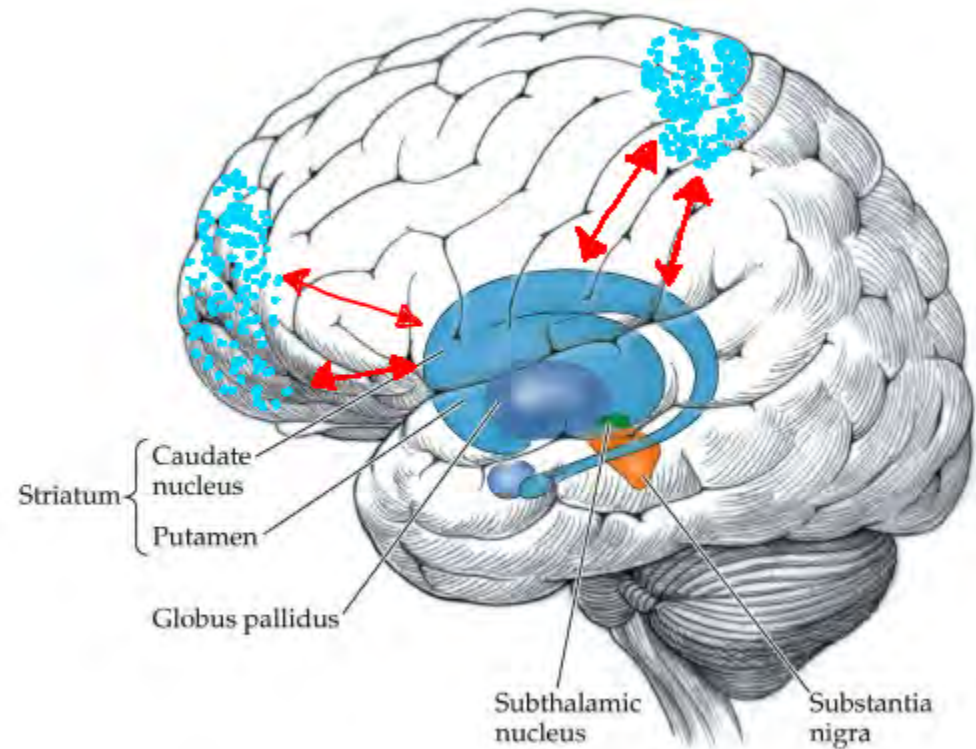
PEA

- Helps with hyperalgesia (severe pain with mildly painful stimulus) and allodynia (pain to touch)
- Mechanism unclear
- It works on the PPAR-alpha receptor and the G-protein coupled receptor 55 (GPR55)
- The PPAR-alpha receptor controls pain and inflammation
- The GPR55 receptor is an endocannabinoid receptor activated by cannabinoids

- Anti-inflammatory
- Prevents mast cell activation (mast cells are important part of inflammation)

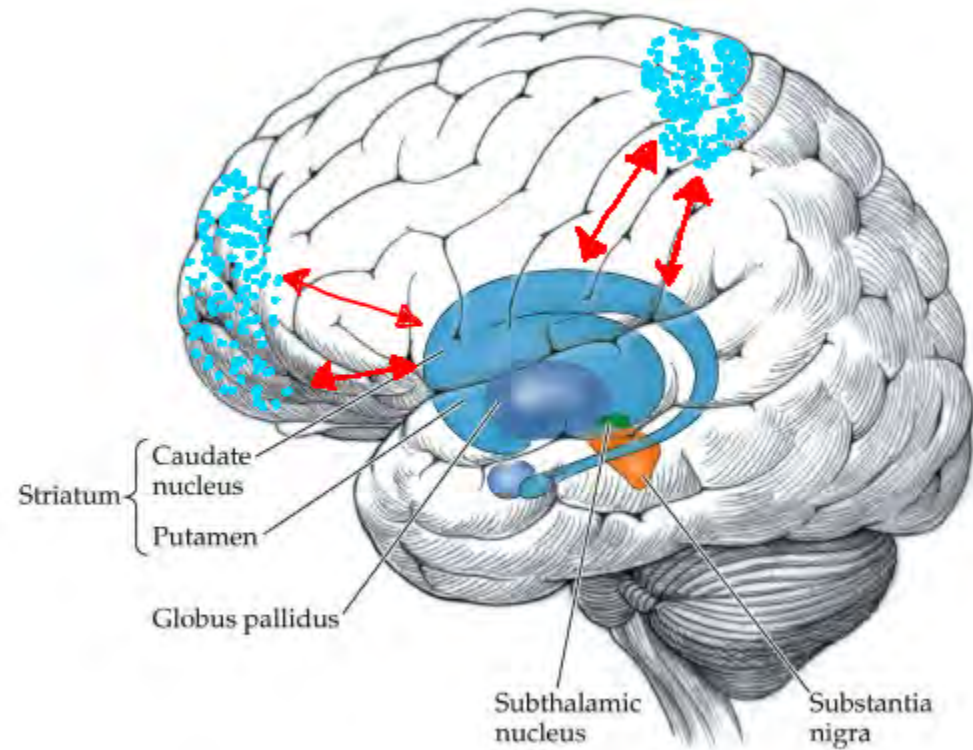
Basal Ganglia

- Part of the brain
- It is associated with different parts of the brain that control movement, cognition and emotion, body perception
- One of the chemicals it uses is dopamine.



Basal Ganglia

- In CRPS – there is reduced dopamine
- Levodopa (Sinemet™) can increase dopamine and may help movement disorders in CRPS
- Dopadura C™ (Germany)
- Carbidopa Lévodopa Teva (France)



Azqueta-Gavaldon et al . Basal ganglia dysfunction in CRPS-a valid Hypothesis?European Journal of pain . 2016
Navani, Journal of Pain and Symptom management. 2003

Muscle dysfunction in CRPS

- Significant muscle issues such as dystonia, tremors, persistent flexion postures of fingers and toes.
- Dystonia is unrelated to Central sensitization and is unlikely to respond to ketamine
- A trial of Baclofen may be helpful

Acknowledgements

- Deutsche Ehlers-Danlos Initiative e.V. www.ehlers-danlos-initiative.de,
- Ehlers Danlos Selbsthilfe e.V. www.eds-selbsthilfe-ev.de,
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- Anke, Deutsche Ehlers-Danlos-Initiative e.V., and Martin, CRPS∞INFO–Forum, www.crps-info.de, for translation of the slides
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- Ellerbrock Conference Technique
- Every helping hand around this event
- Everybody who supports this event with a donation to the organizer

Thank you

Pradeep Chopra, MD

painri@yahoo.com