Osteopathic Manipulation in the Management Autonomic Neuropathy

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Objectives

- Differentiate large fiber, small fiber, & autonomic, polyneuropathy
- Describe features of POTS
- Formulate treatment for autonomic neuropathy using osteopathic manipulation

Roadmap

- Basic Polyneuropathy Review
- Small Fiber Neuropathy Refresher
- Autonomic neuropathy
  - All of this is to argue that OMM has a role in management of dysautonomia
- Some Anatomy of course
- Application of osteopathic manipulation

Polyneuropathy

- Impairment of multiple peripheral nerves
  - Sensory, motor, or autonomic
  - Small, large, or autonomic fibers
- Small fibers
  - Pain and temperature carried on small unmyelinated or thinly myelinated fibers
  - Symptoms: burning or temperature changes
- Large fibers
  - A alpha and A beta large fibers − sensory
  - A gamma − motor
  - Vibration, proprioception, touch/2-point discrimination, loss of bulk
  - Symptoms: tingling, pins and needles

Polyneuropathy

- Large Fiber
  - Axonal, Demyelinating, or Mixed
  - Motor vs Sensory vs Mixed
- Autonomic Neuropathy covered in detail later
  - Carried on unmyelinated or thinly myelinated fibers
- Small Fiber Neuropathy and Autonomic Neuropathy often accompany each other
  - More on this in less than a minute

Polyneuropathy

- Anatomic Distribution
  - Typically length dependent affecting the lower limbs first
  - Think Stocking Glove
    - The glove is usually not affected till the the lower limbs are involved up to the knees
  - There are many exceptions

- A good resource is: https://neuromuscular.wustl.edu

Pathophysiology

- Axonal degeneration
  - most common
  - "Dying back"
    - Most distal part of the axon dies
    - Typical distal symmetric polyneuropathy
    - Usually toxic or metabolic
    - Symptomatic/supportive
- Wallerian degeneration
  - Distal degradation
  - Trauma or nerve infarction
  - Symptomatic/supportive/time
- Segmental demyelination
  - Axon spared
  - Nerve sheath impaired
  - Can be focal mononeuropathy but more often seen in immune mediated/ inflammatory polyneuropathy
  - Medical management

Small Fiber

- Thinly myelinated Aδ
  - Mechanoreceptors and thermoreceptors
  - Pain
  - Cold
  - **Preganglionic fibers (ANS)**
- Unmyelinated C fibers
  - Polymodal receptors
  - Nociception − burning pain
  - Itching
  - Warm
  - Maybe cold
  - **Postganglionic fibers**
    - Sweat glands, blood vessels, heart, etc

Small Fibers

- Sit in the dermis
- Exact pathophysiology of their neuropathy is unknown
  - Autoantibodies to neuronal proteins
  - Inflammatory cytokines
  - Dermal vasculitis

Small Fiber Neuropathy Diagnosis

- Possible
  - Length-dependent symptoms
  - Loss of Pin/temp; allodynia/hyperalgesia
- Probable
  - Length dependent
  - Loss of Pin/temp; allodynia/hyperalgesia
  - Normal NCS
- Definite
  - Length dependent symptoms
  - Loss of Pin/temp; allodynia/hyperalgesia
  - Normal NCS
  - Reduced epidermal nerve fiber density at the ankle (Skin Biopsy) OR abnormal QST (quantitative sensory testing)

Themistocleous AC, Ramirez JD, Serra J, et al. Pract Neurol 2014;14: 368–379.

Small Fiber Neuropathy Etiology

- Metabolic
  - Pre-diabetes/diabetes/abnormal glucose metabolism or rapid correction
  - Vitamin B12 deficiency
  - Dyslipidemia
  - Hypothyroidism
  - CKD
- Immune
  - Sjogren's
  - Celiac
  - Sarcoid
  - RA
  - SLE
  - Vasculitis
  - Inflammatory Bowel Disease
  - Paraneoplastic
  - Monoclonal Gammopathy
  - Amyloid
- Infection
  - HIV
  - Hepatitis C
  - Influenza
- Toxins
  - ARV
  - Antibiotics
  - Chemotherapy
  - Flecanide
  - Statin
  - EtOH
  - Statin
  - Vitamin B6
- Primary Hereditary
  - Nav 1.7 and 1.8 mutations
  - Familial Amyloid Angiopathy
  - Fabry's
  - Tangier's
- Primary Idiopathic
  - Idiopathic SFN
  - Burning Mouth Syndrome

Autonomic Nervous System

- Sympathetic
- Parasympathetic
- Enteric

Sympathetic

- Hypothalamus to the intermediolateral gray cell column in the spinal cord (1st order efferent)
  - Somatotopic organization
- Preganglionic axons from the cord project to the postganglionic neurons (2nd order efferent) on the paravertebral sympathetic ganglia at their level, above, or below
  - 3 cervical, 10-12 thoracic, 4 lumbar and 4-5 sacral
  - Most are paired ganglia

Sympathetic

- Superior cervical ganglion
- Middle cervical ganglion
- Inferior cervical ganglion
  - Inferior can fuse with
    the upper thoracic ganglia

Sympathetic Nervous System

- Caudal most ganglia at the coccyx form the unpaired ganglion impar

Sympathetic Nervous System

- From paravertebral ganglion the sympathetics travel with spinal nerves, cranial nerves, or blood vessel wall to their target

Parasympathetic

- Brainstem and sacrum
- Parasympathetic preganglionic neurons
  - Eddinger-Westphal (III) in rostral midbrain
  - Superior salivatory and lacrimal nuclei (VII) in the pontine tegmentum
  - Inferior salivatory nucleus (IX) periventricular gray – rostral medulla
  - *Nucleus ambiguus (X) – medulla reticular formation posterior to the inferior olivary nucleus*
    - *Oropharynx*
  - *Dorsal Motor Nucleus (X) – floor of the forth ventricle*
    - *Thorax and abdomen*
  - **CN X has the largest group of parasympathetic fibers in the body**

Nucleus Tractus Solitarius

- Receives sensory input from a number of cranial nerves including Vagus.
- Carotid body, aortic bodies, SA node via the vagus
- Taste, sensation to the middle ear
- Receives input from the heart, lungs, GI, liver, etc
- There is a lot of vagal tone set through here because of this
- Autonomic Reflex zone

Dorsal Motor Nucleus X

- Please reference Netter

ANS

- Bidirectional connected between target and central autonomic network
- Central Autonomic Network (CAN)
  - Medial prefrontal cortex
  - Insular cortex
  - Central nucleus of the amygdala
  - Hypothalamus
  - Periaqueductal gray
  - Parabrachial nuclear complex
  - Nucleus Ambiguus
  - Nucleus Tractus solitarius
- R. Paul Lee, DO describes a release for this CAN
  - We will not do it here

ANS Dysfunction

Dry Mucus membranes
Anhydrosis
Abnormal pupils
Constipation/Diarrhea
Vomiting
Abdominal pain
Early satiety/anorexia
Intestinal pseudo-obstruction
Urinary retention
Skin color changes
Abnormal heart rate
Orthostasis
Erectile dysfunction

Etiology

- Diabetes
- Multisystem Atrophy
- Guillain-Barre
- Sjogren's Syndrome
- Paraneoplastic
  - Small cell lung cancer
- HIV
- Botulism
- Chagas (now in the US)
- Diphtheria
- Leprosy
- Rabies

- Acute Dysautonomia
- Parkinsonism
- Neuronal intranuclear inclusion disease
- Myopathy and external ophthalmoplegia, neuropathy, gastro intestinal encephalopathy
- A number of hereditary conditions

Autonomic Nervous System

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

POTS

- These patients range from mildly impaired to bedridden
- They were usually normal productive people before
  - This can be lost on the medical system
  - In severe cases their lives are usually destroyed and they just want to be normal
  - *Labeled psychiatric*
  - Symptoms confused with anxiety
    - Especially since it affects women more than men
- They will search for exotic diagnoses
- They will need a lot of hand holding and TLC
- Severe cases may take years to recover
  - 1 year OMM, 1 year PT, then additional OMM

POTS - Autonomic Neuropathy

- Some estimates are that 1% of US population has POTS
- Heart rate increase ≥30 bpm within 10 min of upright posture in adults. Heart rate increase of ≥40 bpm within 10 min is required in adolescents age 12–19 years
- Absence of orthostatic hypotension defined as a sustained drop in blood pressure ≥ 20/10 mm Hg within 3 min of upright posture
- Symptoms of orthostatic intolerance for ≥6 months
- Absence of overt causes for sinus tachycardia such as acute physiological stimuli, dietary influences, other medical conditions and medications
- Tilt table test with or w/o sudomotor testing and transcranial doppler

POTS

- Female:Male 4:1
- Typically 13-50 years old
- **13% with family history**
- Heterogeneous (Cardiogenic vs neurogenic vs **structural***)
- Start after acute stress
  - Surgery, viral illness, MVC etc.
- Blurry vision, brain fog, cognitive dysfunction, chest pain, lightheaded, nausea, fatigue, constipation, acrocyanosis, sleep abnormalities, anxious/brainstem feeling
- Only about 30% have syncope
- Look for **Ehler's Danlos Type III***, Mast Cell Activation Syndrome, Chronic Fatigue Syndrome, migraine, fibromyalgia, Sjogren's and other autoimmune conditions, GI problems (bloating, chronic constipation)

Pathophysiology

- 50% of POTS patients have distal small fiber neuropathy with sympathetic denervation
  - Patient may not be aware of the neuropathy
  - Impaired peripheral vascular resistance in the legs when standing due to blunted norepinephrine there
    - Causes excessive venous pooling →
    - Sympathetic activation →
    - Increase heart rate to maintain blood pressure

Pathophysiology

- 50% have **Hyperadrenergic state**
- Excessive orthostatic tachycardia
- Might be related to excessive interleukin-6
- Usually from hypovolemia or partial sympathetic denervation
- Test orthostatic catecholamines 15 minutes supine then 15 minutes standing (okay to lean against a wall)

Pathophysiology

- Norepinephrine transporter deficiency
  - Causes loss of sympathetic activation by decreasing amount of NE taken up at the synapse
  - Gene SLC6A2
  - Tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, atomoxetine impact NET

Pathophysiology

- Hypovolemia
  - Low blood volume with decreased red blood cell count
  - 13% deficit in plasma volume in POTS
- Thought to cause lower stroke volume and compensatory tachycardia
- Impaired vascular and renal response to hypovolemia
  - Angiotensin II levels are high and BP is normal
- **Fluid responsive**
  - Give Lactated Ringers or isotonic saline
  - Oral rehydration

- Please reference Arnold et al. Postural tachcardia syndrome − diagnosis, physiology, and prognosis. Autonomic Neuroscience: Basic and Clinical. 2018. https://doi.org/10.1016/j.autneu.2018.02.005
- Figures 3 and 4

Pathophysiology

- Immune mediated (some studies show 20%)
- Antibodies to ganglionic acetylcholine receptor
- Antibodies to alpha 1 and beta adrenergic receptors and cardiac lipid proteins
- Non-specific markers (e.g, ANA) positive in 25% while 31% have some antibody +
- IgG against cardiac proteins
  - 40 identified

POTS association:

- Sjögren syndrome
- Ankylosing spondylitis
- Antiphospholipid syndrome
- Behcet's disease
  Celiac disease
- Chronic immune demyelinating polyneuropathy
- Inflammatory bowel disease (Crohn and ulcerative colitis)
- Hashimoto's thyroiditis
  Multiple sclerosis
  Neuromyelitis optica
  Rheumatoid arthritis
  Sarcoidosis
  Systemic lupus erythematosus
  Juvenile rheumatoid arthritis
  Adult Still's disease
  Undifferentiated connective tissue disease

Pathophysiology

- Impaired cerebral autoregulation
- Orthostatic intolerance despite normal blood pressure
  - Is this problem central rather than peripheral?

Pathophysiology

- Deconditioning − not sure if this is primary or secondary
- Aerobic exercise is critical
- Is the heart too small?

Structural Associations

- Thoracic Outlet Syndrome
  - Stellate ganglion compression?
- Hypermobility – Ehlers Danlos type 3
  - Also associated with Mast Cell Activation Syndrome
- Maybe Chiari Malformation
- Eagle syndrome
  - Elongated styloid
  - Compression of CN X, IX, carotid

Structural Associations

- Median arcuate ligament syndrome
  - intermittent obstruction of celiac or superior mesenteric arteries by the median arcuate ligament
    - celiac plexus compression
  - postprandial or post-exertional abdominal pain
- Pelvic vein varicosities
  - Venous pooling

A role for the Vagus Nerve in Treatment?

- Vagal nerve stimulation
  - Anti-inflammatory
  - Shown to improve rheumatoid arthritis, Crohn's, Sjogrens
- Regular exercise improves vagal tone
- Anti-inflammatory diet
- Acupuncture
- Biofeedback
- Music therapy
- Meditation

Treatment

- A great cardiologist or autonomic neurologist
- Increased sodium and fluid intake
- Compression stockings
- **Aerobic exercise**
- Isotonic saline/Lactated Ringers infusions
- Beta blockers
  - Metoprolol
  - Corlanor
- Alpha 1 agonist: Midodrine
- Florinef in some cases
- L-Dopa, carbidopa
- SSRI/SNRI
- IVIG/Plasma Exchange/steroids/Rituximab

POTS Additional Information

- Arnold et al. Postural tachcardia syndrome − diagnosis, physiology, and prognosis. Autonomic Neuroscience: Basic and Clinical. 2018. https://doi.org/10.1016/j.autneu.2018.02.005
- Vernino and Stiles. Autoimmunity in postural orthostatic tachycardia syndrome: current understanding. Autonomic Neuroscience: Basic and Clinical. 2018. https://doi.org/10.1016/j.autneu.2018.04.005
- Goodman. Evaluation of postural orthostasis tachycardia syndrome (POTS). Autonomic Neuroscience: Basic and Clinical. 2018. https://doi.org/10.1016/j.autneu.2018.04.004
- Wells et al. Postural tachycardia syndrome: current perspectives. Vascular Health and Risk Management. 2018:14; 1-11.

POTS

IS THERE A ROLE FOR OMT?

OMT for POTS

- Goodkin and Bellew 2014 describe OMT for POTS
  - 26 year old female with fatigue, pre-syncope, heat intolerance, cognitive dysfunction, diffuse joint pain, insomnia, jaw injury
  - POTS diagnosed, partial response to Florinef, midodrine
  - Ligamentous articular strain
  - Osteopathic cranial manipulative medicine
  - **Pre-treatment – could only tolerate 5 minutes in a hot shower**
  - **Post treatment – 45 minutes**
  - Was able to reduce midodrine and amphetamine for 8 days
  - Treated again and this time improved for 8 weeks
  - Treated a 3rd time 28 days later and remained controlled at her 18 month follow-up
  - JAOA Nov 2014;114:874-877

OMT for POTS – GI symptoms

- Cromeens and Gambler 2010
- 48 year old male with decade of post-prandial abdominal bloating, cramping, nausea and vomiting, and POTS, spine pain throughout
- By the 3rd treatment patient had reduced GI symptoms
- 4th Treatment decreased pain
- Required maintenance treatment
- Soft tissue, muscle energy, articulatory, ligamentous articular strain, integrated neuromuscular release, articulatory techniques

- Osteopathic Family Physician 2010;2:144-147

Polyneuropathy

OSTEOPATHIC MANIPULATION TECHNIQUES

Osteopathic Manipulation

- Large fiber neuropathy
  - **Best to treat the underlying cause**
  - However Treatment of CSF, epineural space and perineural space might be helpful

Today's Lab will focus on Vagus But…

- Autonomic Neuropathy
  - Linea Alba release
    - Release the celiac ganglion and plexus while you are there
  - Correct dysfunction of the respiratory and pelvic diaphragm
  - CV4, might need lots of them
  - Treat ANS and structural abnormalities
    - **Treat the occiput/OA, sacrum, coccyx,**
      - **When the patient is healthy enough integrate the systems**
      - Treat the ganglion impars
        - » Treating hand on the sacro-coccygeal junction and tip of coccyx
      - Treat midline of the sacrum
      - Release the sympathetic chain there
    - Treating the vagus nerve and its nuclei (next slide)

For Images

- Please reference: Netter
- Blumenfeld: Neuroanatomy through Clinical Cases

Vagus Nerve Anatomy

- Exits Medulla
  - Between olive and inferior cerebellar peduncle
- Jugular foramen
  - Sensory ganglia
    - Superior and inferior
- Joins CN XI below the inferior sensory ganglion
- Descends through the carotid sheath posterolateral to carotid
- Medial to internal jugular vein

Right Vagus

- Crosses anterior to subclavian artery
- Fat behind the innominate vessels
- Enters thorax right of the trachea
- Rises behind the hilum of the right lung
- Courses medially toward esophagus
  - Joins the left vagus to form the esophageal plexus

Left Vagus

- Crosses anterior to the left subclavian artery
- Enters the thorax between the left common carotid and subclavian arteries
- Descends on left side of the aortic arch
- Behind the phrenic nerve
- Behind the root of the left lung
- Medially and downward to esophagus
- Meets right vagus → esophageal plexus

Vagus: Gastric Nerves

- Esophageal plexus gives rise to the anterior and posterior gastric nerves
- Supply all abdominal organs and GI tract to the splenic flexure
- Right vagus → posterior gastric plexus
  - Posterioinferior
- Left vagus → anterior gastric plexus
  - Anterosuperior

Vagus: Celiac Nerve

- Right vagus nerve
- Celiac plexus

Vagus and the Heart

- Esophageal plexus
  - Supplies posterior pericardium
- Invests in the deep cardiac plexus
  - Anterior to carina
  - Inferior cardiac branch
    - Right side from trunk of vagus at the trachea
    - Left from recurrent laryngeal nerve

Cardiac Plexus

- Superficial
  - Under the aortic arch anterior to the right pulmonary artery
  - Left sympathetic trunk and lower superior cervical cardiac branch of the vagus
- Deep
  - Anterior to the carina, posterior to aortic arch
  - Mix of sympathetic from the and parasympathetic from inferior cardiac branch of vagus

Deep Cardiac Plexus

- Right side
  - Anterior and posterior coronary plexus
  - Right atrium
- Left side
  - Superficial cardiac plexus
  - Left atrium
  - Posterior coronary plexus

Okay let's treat

- Occipitocervical hold or vault − just be comfortable − treat by intention, if you need to treat locally, hands anterior chest wall at the level of the carina (sternal angle) and epigastric area is fine
- DO NOT INVADE; DO NOT RUSH
- Get on the 4th ventricle
- Move anterior and find dorsal motor nerve of the vagus
  - Just lateral to the hypoglossal nucleus − pick one side to treat first then bring in the other
- Bring your attention to the esophageal plexus − bridge to the dorsal motor nucleus of the vagus
- Now bring your attention to the anterior and posterior gastric plexus
- Bridge it to the esophageal plexus then the dorsal motor nucleus
- Now bring your attention to the celiac plexus and do the same as above
- Bring your attention to the superficial and deep cardiac plexus − treat and integrate with the esophageal plexus
- Now see the big picture and put it all together
- Now release the nucleus tractus solitarius then nucleus ambiguus
- THIS IS TOO BIG A TREATMENT FOR A SICK PATIENT
  - Treat the individual components first and over time start linking them together