MCAS, Post-Viral Concerns, hEDS, POTS, and other Conditions that May Impact Spinal CSF Leak Diagnosis,Treatment, and Healing

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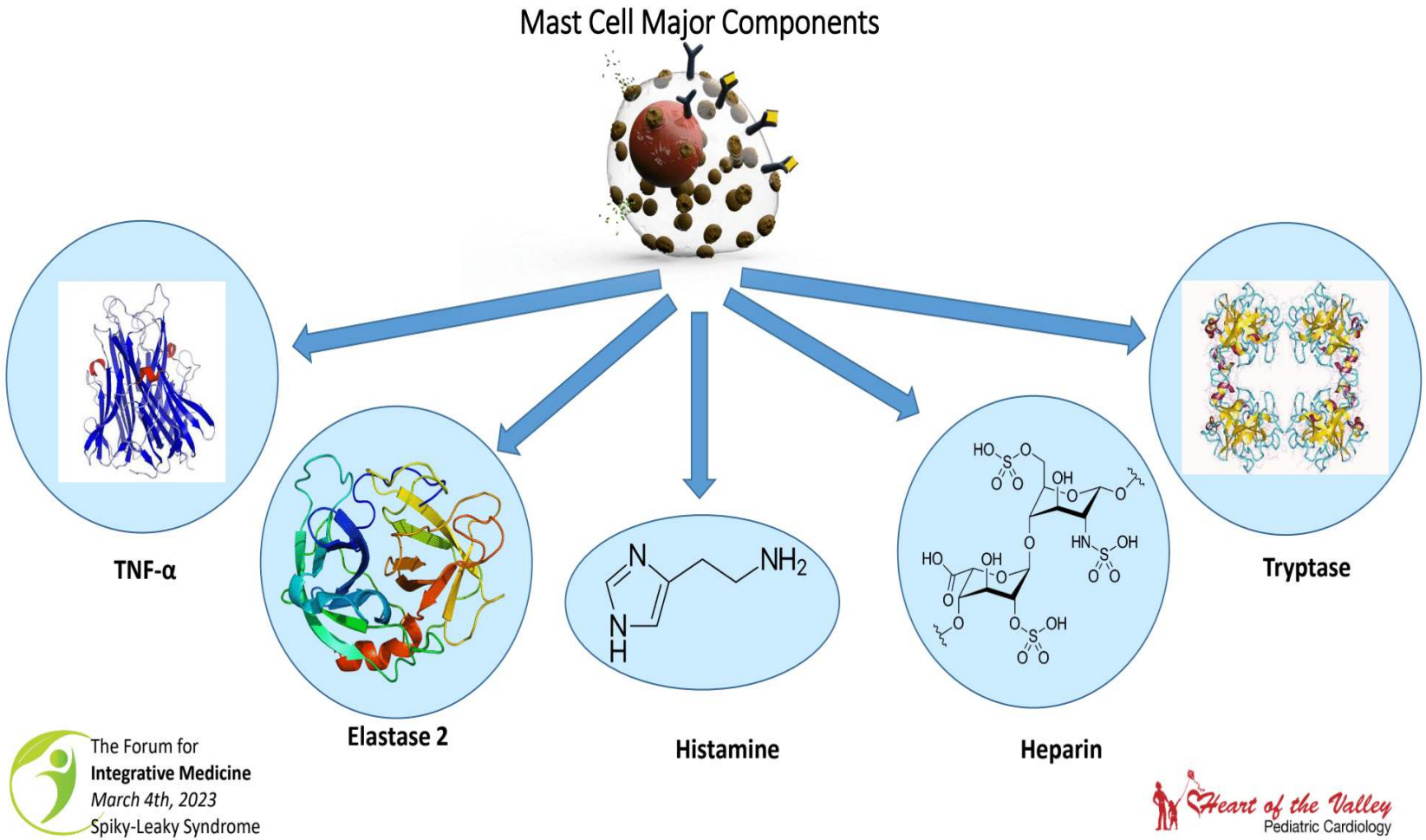
- No disclosures or conflicts

MAST CELL ACTIVATION SYNDROME (MCAS)

- A chronic multi-system/multi-organ illness presenting with widely varied and often confusing
- An acute and/or chronic inflammatory syndrome caused by the release of over 1200 mediators from Mast Cell degranulation
- Triggers can range from infection, autoreactivity, food, excipients, sunlight, noise, water, smells, exertion, pain, mechanical pressure

- Mast Cell Activation Syndrome



MCAS

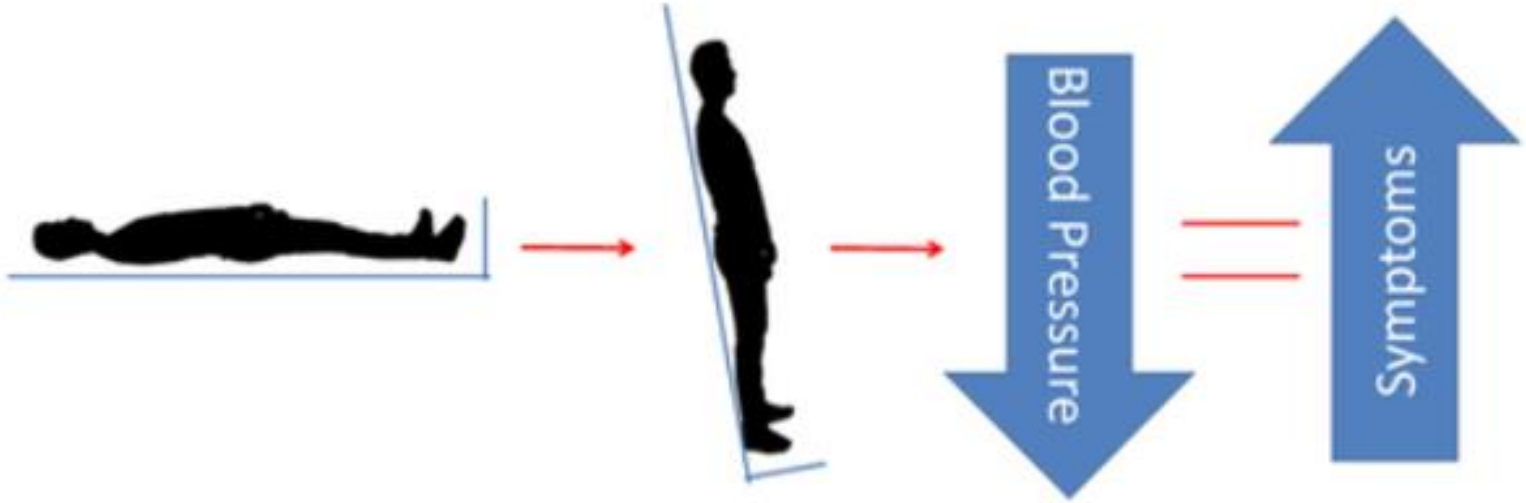
- When mast cells are in the presence of astrocytes in the perivasculature, they release histamine, leukotrienes, and cytokines
  - Via CD40-CD40L (Kim et al. 2010, 2011)
  - Astrocytes have Histamine receptors and release cytokines that further induce mast cell degranulation (Dong and Benviste 2001)
    - Implications for BBB (Skaper, 2016; Ribatti D., 2015)
    - Dura mater packed with mast cells (Balcziak et al 2022)
- PAMPs and ATP activate glia
  - Release IL-33, IL-1beta, IL-13 (Bulanova and Bulfone-Paus, 2010, Kim et al., 2010)
- Proteases that degrade collagen as well as myelin

Postural Orthostatic Tachycardia Syndrome (POTS)

- The normal response to standing, via the baroreflex, is a small fall in systolic BP , a rise in diastolic pressure, and a rise in heart rate
- Baroreflex sensitivity is higher in hypermobile patients
- Higher incidence of Orthostatic Intolerance
  - Neurogenic Orthostatic Hypotension
  - **Postural Orthostatic Tachycardia Syndrome**
    - **Blood pressure maintained by a compensatory tachycardia**
    - **Increases cardiac output**
  - Vasovagal Syncope

Neurogenic Orthostatic Hypotension (nOH)

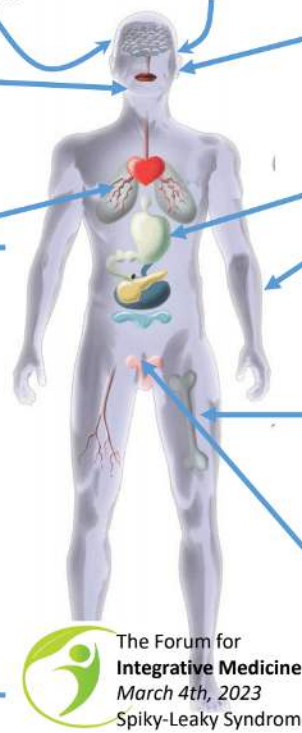
- Sustained reduction of blood pressure
  - >=20 mmHg systolic
  - >=10 mmHg diastolic
  - Occurring within 3 minutes of standing or head-up tilt (HUT)



“Passive standing”

Dysautonomia Drives Disease

- Dysautonomia



Head
Orthostatic Sx:
- Dizziness*
- Light-headedness
- Near-syncope*
- Syncope

Salty, Metallic clear fluid
- Nose
- Ears
- Back of throat

Pain:
- Migraine
- Non-migraine
- Occipital
- Neck Pain
- Coat-hanger Pain

Mind
- Attention deficit*
- Foggy Thinking*
- Anxiety*
- Panic Attacks
- Depression
- Irritability
- Hallucinations
- OCD
- Tics

Sleep
- Insomnia*
- Sleep-disordered breathing
- Apnea
- Sleep Paralysis
- Altered sleep architecture
- Narcolepsy

Vision/Hearing
- Blackout/whiteout/spotty vision*
- Visual hallucinations
- Sensitivity to textures
- Sensitivity to light
- Sensitivity to sound
- Ringing in ears
- Vertigo (room spinning)
- Hyperacusis (sounds are too loud)
- Phonophobia (dislike noise)

Abdomen
- Nausea*
- Early Satiety
- Indigestion
- Excessive Food sensitivities
- Cyclic vomiting
- Bloating
- Reflux (heartburn)
- Constipation
- Diarrhea

Pain:
- Sharp epigastric
- Crampy generalized

Chest
Racing heart
- Bursts (Palpitations)*
- "Rushes of Flushes"
- Recumbent racing heart
- Chronic racing heart

Shortness of breath
- Dyspnea
- Hyperventilation sequence

Pain:
- Chest pain
- Globus (mass in throat)
- Stabbing pains in throat

Extremities
- Accrual coldness*
- Raynaud's syndrome

Dyshydrosis:
- Hyper-hydrosis
- Anhydrosis

- Distal leg/foot pooling
- Restless legs

Musculoskeletal
- Muscle weakness*
- Generalized muscle cramps
- Joint hypermobility
- Joint dislocations
- Joint Subluxations
- TMJ Dislocation

Pain:
- Generalized muscle pain
- Generalized bone pain
- Stabbing pain in throat
- Multiple joint pains
- TMJ Pain
- Back pain

Systemic
- Generalized Fatigue*
- Early exhaustion
- Exercise intolerance*
- Intolerance to upright position
- Chronic fever
- Tremulousness/shakiness

Temperature dysregulation
- Feeling hot*
- Feeling cold*

- Hyper-allergenic

Genitourinary
- Urinary frequency*
- Chronic UTI (sterile)
- Incontinence
- Difficulty starting urination
- Inability to finish urination
- Vaginal Bleeding
- Dysmenorrhea

Pain:
- Endometriosis
- Dyspareunia

SKIN
- Cyanosis and Pooling
- Hives
- Easy rashing
- Livido Reticularis
- Dyshidrotic eczema on palms and soles
- Easy Bruising

The Forum for **Integrative Medicine**
March 4th, 2023
Spiky-Leaky Syndrome

Heart of the Valley Pediatric Cardiology

Postural Orthostatic Tachycardia Syndrome (POTS)

Sustained increased heart rate of 30 bpm within 10 min of standing or HUT

AND

Symptoms of cerebral hypoperfusion or sympathetic activation

Approximately 1/3 of patients with POTS also experience vasovagal syncope associated with position change

Common co-morbidity is joint hypermobility

POTS Symptoms

- Tachycardia – Cardinal Feature
- Palpitations
- Dyspnea
- Tremulousness
- Lightheadedness
- Diaphoresis
- Nausea
- Headaches
- Blurred vision
- Pallor
- Coat Hanger Pain
- Anxiety
- Fecal urgency
- Brain fog

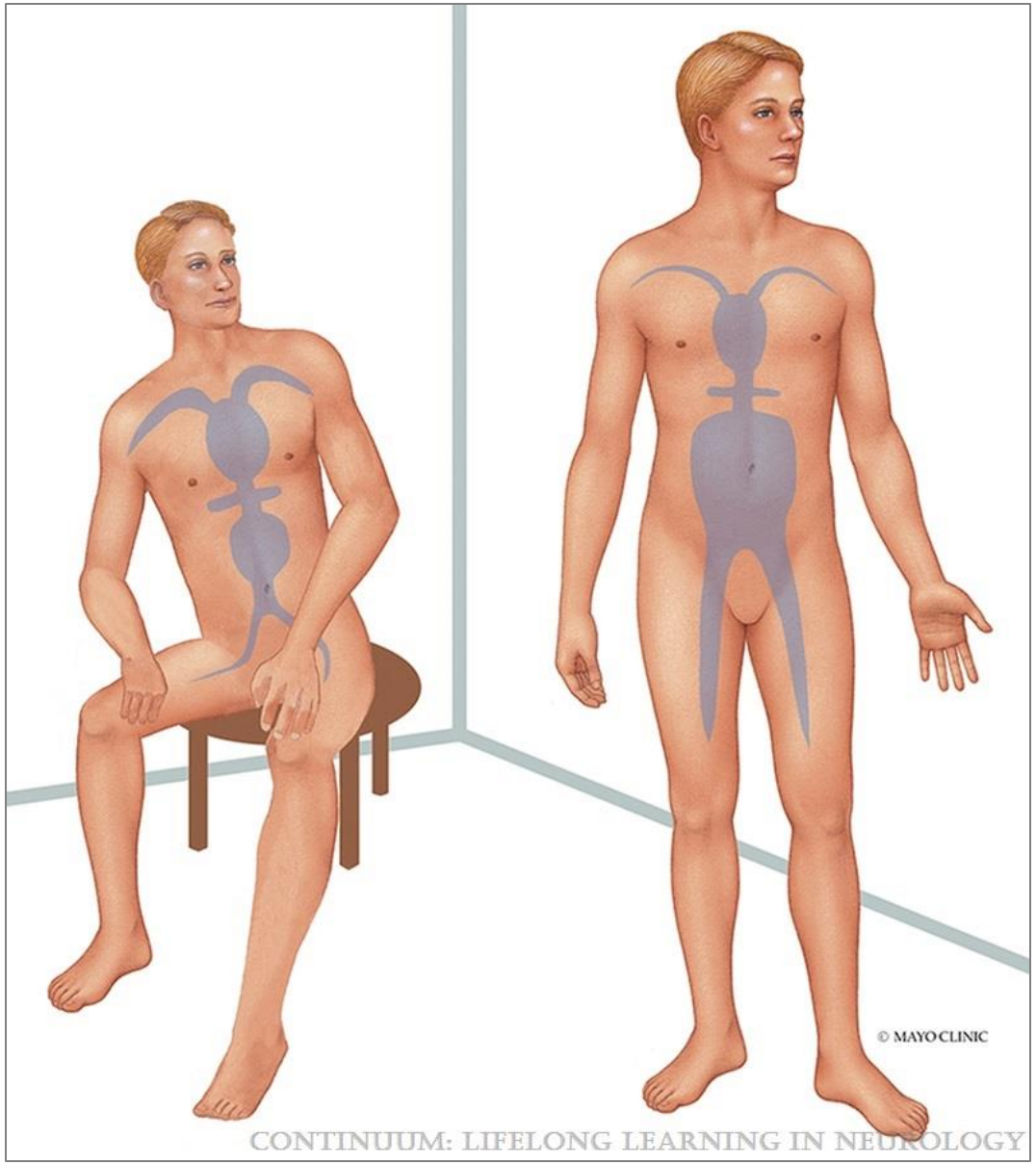
POTS

- Many patients have non-orthostatic symptoms
  - Chronic fatigue
  - Circadian rhythm disorders
  - Gastrointestinal difficulties
  - Interstitial cystitis
  - Exercise Intolerance
  - Fatiguability

POTS

- Symptoms exacerbated by:
  - Medications
    - TCAs, SSRIs, Stimulants, Anti-hypertensives
  - Prolonged recumbency
  - Heavy meals
  - Heat exposure
  - Intense physical activity
  - Illness

FIGURE 2-1



[Autonomic History, Examination, and Laboratory Evaluation]

Cheshire, William P. Jr

CONTINUUM: Lifelong Learning in Neurology26(1):25-43, February 2020.

doi: 10.1212/CON.0000000000000815

Radial pulse can become difficult to palpate
Acral coldness, swelling, blueness

Schema of orthostatic venous blood redistribution. Upon standing, the force of gravity pulls 500 mL to 800 mL of blood downward. If unopposed by the autonomic nervous system, thoracic venous blood is redistributed toward the abdomen, pelvis, and proximal lower extremities, and venous return to the heart declines.

POTS Mechanisms

- **Volume Dysregulation**
  - Hypovolemia
    - Reduced cardiac preload, unload baroreceptors, results in sympathetic outflow
  - Venous Pooling
    - Compression Garments
  - Capillary Leakage
- **Impaired cerebral autoregulation**
  - Cerebral hypoperfusion from reduction of CBF velocity during HUT
    - Paradoxical cerebral arteriolar vasoconstriction

POTS Mechanisms

- **Hyperadrenergic State**
  - Excessive sympathoexcitatory response
    - Triggered by standing, exercise, emotional stimuli
      - May occur during sleep
      - Primary and secondary
- **Neuropathic**
  - Impaired sympathetically mediated vasoconstriction in lower limbs due to adrenergic and sudomotor denervation
    - Results in venous pooling
  - α_3 subunit of ganglionic nicotinic AchR antibodies leads to autoimmune autonomic ganglionopathy
- **Deconditioning**
  - Exercise Intolerance
  - Greater and persistent tachycardia
  - Some with reduced stroke volume and left ventricular mass

Connective Tissue

- Connective tissue forms the scaffold for organized structure and growth in the body
  - Also controls cell adhesion, cell migration, and tissue repair
- EDS is classic inherited connective tissue disorder
  - Defects in architecture and metabolism of fibrillar collagens, modifying enzymes, ECM molecules (Parapaia and Jackson, 2008)
- In 1900s, Ehlers and Danlos noted a triad:
  - Skin fragility
  - Skin hyperextensibility
  - Joint hyperextensibility
- Other organ involvement over time was noted
  - Ocular, cardiovascular, respiratory, gastrointestinal, CNS, PNS

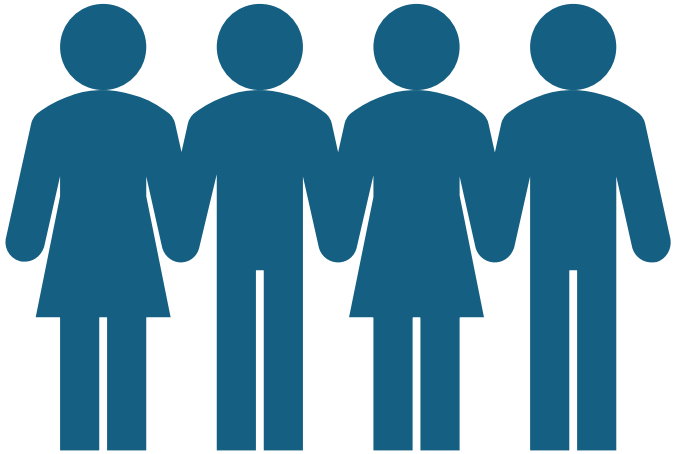
Hypermobility Ehlers Danlos Syndrome (hEDS) (and other connective tissue disorders)

- Dural weakness
  - Mokri B, Maher CO, Sencakova D. Spontaneous CSF leaks: underlying disorder of connective tissue. Neurology. 2002 Mar 12;58(5):814-6. doi: 10.1212/wnl.58.5.814. PMID: 11889250.
  - "**Joint hypermobility was overrepresented in our study as 49% of the (229) participants with MECFS had a Beighton score >4 compared to 3% in the general population.**" Bragee et al., 2020.

- Bragée B, Michos A, Drum B, Fahlgren M, Szulkin R, Bertilson BC. Signs of Intracranial Hypertension, Hypermobility, and Craniocervical Obstructions in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Front Neurol. 2020 Aug 28;11:828. doi: 10.3389/fneur.2020.00828. PMID: 32982905; PMCID: PMC7485557.

Some facts about EDS

- Prevalence: EDS has an estimated prevalence of 1 in 5,000 individuals worldwide
- In past year, ~284 research papers on hypermobility compared with ~880 between 2019-2023
- There are several different types of EDS, with the most common being hypermobile EDS, classical EDS, vascular EDS
- EDS can often be challenging to diagnose due to its wide range of symptoms and overlap with other conditions. Genetic testing and clinical evaluation are typically used to diagnose EDS.
- Treatment for EDS focuses on managing symptoms and preventing complications. This may include physical therapy, pain management, co-morbid diagnosis management, and lifestyle modifications.



Heritable connective tissue disorders (HCTDs)

- Over 450 recognized – not just EDS
  - Marfan syndrome, Loeys-Dietz syndrome, Stickler syndrome
  - Osteochondrodystrophies
  - Glycosaminoglycan Disorders
- Cells of connective tissue include fibroblasts (produce the collagen), adipocytes, chondrocytes, osteocytes, mast cells, macrophages, leukocytes, erythrocytes
- Arises from the mesenchymal cell lineage
- Present all over the body including the nervous system
  - Meninges, Glial cells, vessel walls
- In addition to fibers and cells, there is also extracellular matrix (ECM) which has non-structural collagen fibers as well proteoglycans, mucopolysaccharides, and glycoproteins
  - ECM mediates exchange between the circulation and other tissues of the nutrients , O_2, CO_2, and waste by-products; metabolite transfer

Connective Tissue

- Human body has muscular, epithelial, neural, connective tissues
  - Connective tissue most abundant and diffusely present
  - Structural and mechanical functions
    - Strengthens, supports, binds, buffers, protects
  - Different composition based on anatomical region/organ
- Overall supports functioning of all body tissues
  - Location of individual anatomical components are genetically predetermined
  - Human body is a cohesive network of tissues
- Most abundant fiber is collagen protein
  - 30% of total protein mass; ~4 kg
  - Malek and Koster (2021) found disorganized collagen bundles and abnormal cellular mechanisms of fibroblasts in EDS/HSD
  - Defects in fibrillar collagens

Connective Tissue

- Schievink, Wouter I. M.D.; Gordon, Ora Karp M.D.; Tourje, James M.D.. Connective Tissue Disorders with Spontaneous Spinal Cerebrospinal Fluid Leaks and Intracranial Hypotension: A Prospective Study. Neurosurgery 54(1):p 65-71, January 2004. | DOI: 10.1227/01.NEU.0000097200.18478.7B

- Findings suggesting connective tissue disorders are common among patients with spontaneous spinal CSF leaks, and manifestations may be subtle. A variety of disorders can be identified, probably reflecting genetic heterogeneity. Problems with wound healing may occur as a result of the systemic nature of the underlying connective tissue disorder.

Connective Tissue Disorders and the Spine

- Chiari malformation Type I (Henderson et al., 2017)
- Atlantoaxial Instability (Halko et al., 1995)
  - Can lead to high cervical myelopathy
- Craniocervical Instability
  - Can affect brainstem and spinal cord through direct pressure (CMS), vertebral artery involvement, or change in CSF flow (Celletti et al., 2012)
- Basilar invagination
  - Can also cause CMS
- Segmental instability and kyphosis (Isaac and Das, 2022; Muhle et al., 1998)
  - Often causes myelopathy through buckling of the ligamentum flavum
- Tethered Cord Syndrome
- Tarlov Cysts Syndrome

Cranial Cervical Instability (CCI)

- CCJ contains cervicomedullary anatomy
  - Medulla oblongata
    - Medullary kink
  - Cervicomedullary syndrome
  - Lower cranial nerve involvement
- This junction also includes the vertebral arteries, basilar artery, first and second cervical nerve roots, CSF compartment flow

Cranial Cervical Instability (CCI)

- Ligaments are the major occiput-C1 stabilizing structures
- Most mobility of any other section of spine
  - Denticulate ligaments
    - More robust collagen tissues
  - Transverse ligament of the atlas constrains the dens
    - With its crura forms the cruciate ligament
    - Contributes significantly to the stability of the junction
  - Alar ligaments from the dens attach to the condyles
    - Further maintain stability of junction

Cranial Cervical Instability (CCI)

- Milhorat et al. showed unique mobility and morphometrics in patients with Chiari and EDS compared to those with CM1 only or healthy controls
  - Clivus-axial angle (decrease)
  - Atlas-axis angle (decrease)
  - Clivus-atlas angle (decrease)
  - Basion-dens interval (BDI) (decrease)
  - Basion-atlas interval (BAI) (increase)

Spontaneous CSF leaks

- Meningeal diverticula
- Dural tear
- Dural venous fistula
- Tarlov cysts
- Indeterminate

Post-Viral Syndromes

- ME/CFS
- Post Covid Syndrome (“Long Haulers”)
- Post Viral Fatigue Syndrome (SARS, MERS, Dengue, Zika, Ebola)
- Chronic Lyme Disease

Autoimmune Disease

- The dura mater is densely packed with macrophages, mast and dendritic cells, and they have been found to associate with meningeal blood vessels and trigeminal afferent endings (Balcziak et al. 2022)
- Immune cells dispersed provide avenues for antigen detection to causes inflammatory and immune responses

Risks of poor healing

- Open communication of the subarachnoid space with CSF leak presents a pathway for life-threatening CNS infection
  - Soni AJ, Modi G. Outcome of uncorrected CSF leak and consequent recurrent meningitis in a patient: a case presentation and literature review. Br J Neurosurg. 2020 Oct;34(5):492-494. doi: 10.1080/02688697.2018.1478063. Epub 2018 May 28. PMID: 29807467.
  - Dobrocky T, Nicholson P, Häni L, Mordasini P, Krings T, Brinjikji W, Cutsforth-Gregory JK, Schär R, Schankin C, Gralla J, Pereira VM, Raabe A, Farb R, Beck J, Piechowiak EI. Spontaneous intracranial hypotension: searching for the CSF leak. Lancet Neurol. 2022 Apr;21(4):369-380. doi: 10.1016/S1474-4422(21)00423-3. Epub 2022 Feb 25. PMID: 35227413.

Questions/contact

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