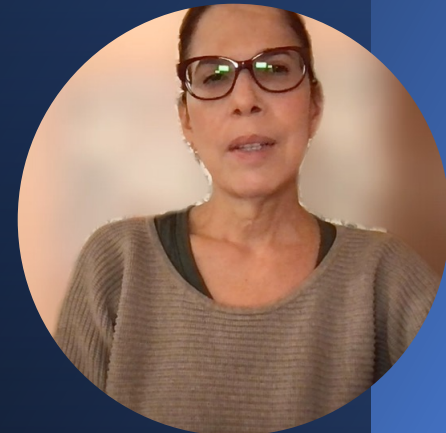


The Approach to the Complex Patient

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- Ilene Ruhoy has no Disclosures or Conflicts



What is a Complex Patient?

- Chronic and debilitating symptoms
 - Unclear single pronged etiology
 - Thwarts easy treatment and management attempts
 - Multi-factorial
 - Leads to several diagnoses
 - CTD, EDS, MCAS, SFN, CCI, IIH, etc.
 - Septad
- Does not easily localize
 - Systemic contribution to symptoms and disability
 - CSF leak patients often have evidence of other connective tissue compromise



Connective Tissue Disorders

- Connective tissue disorders
- Heritable and acquired
- 13 clinical EDS subtypes recognized comprising defects in 19 different genes
 - Defects in architecture and metabolism of fibrillar collagens, modifying enzymes, ECM molecules (Parapaia and Jackson, 2008)
- Hypermobility type (HSD)
 - Molecularly elusive



Connective Tissue Disorders Symptom Complex

Estimated 1/5000 affected (Gensemer et al., 2021)

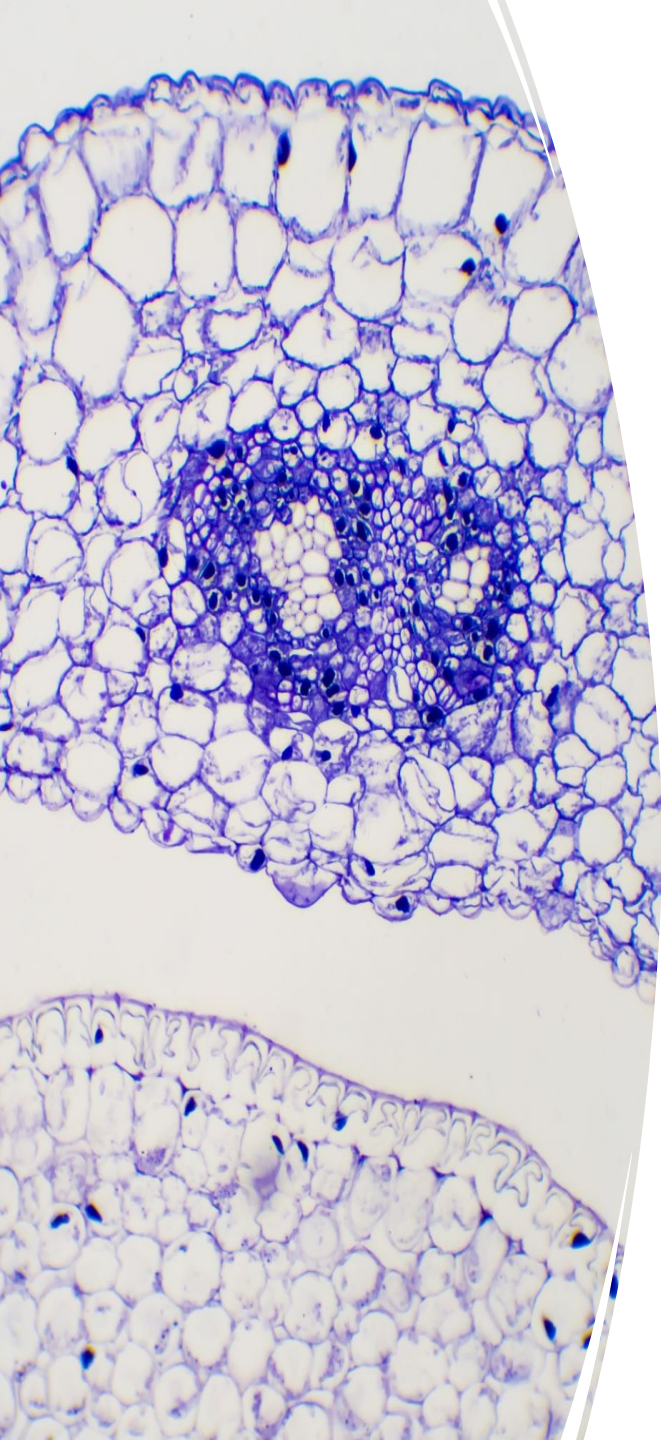
Manifestations (Tinkle et al., 2017)

- Symptomatic Joint Hypermobility
- Pain
- Skin manifestations
- Fatigue
- Cardiovascular
 - POTS, OI, MVP, dilation of aortic root
- Gastrointestinal
- Dysautonomia
- MCAS
- Bone mass
- Headaches
- TMJ/Periodontal issues
- Spine
- Gynecologic Issues
- Pelvic Dysfunction
- Sleep Disturbance
- History of recurrent infections and exposures



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
 - Also has elastic and reticular fibers



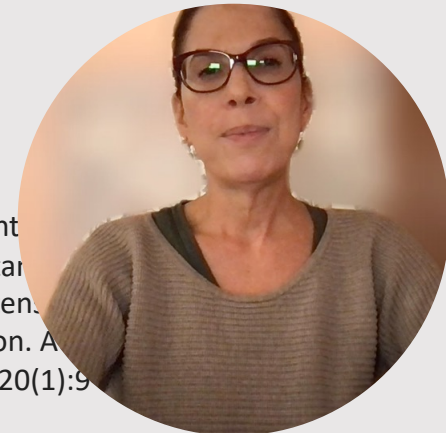
Connective Tissue

- Cells of connective tissue include fibroblasts (produce the collagen), adipocytes, chondrocytes, osteocytes, mast cells, macrophages, leukocytes, erythrocytes
- Arises from the mesenchymal cell lineage
- 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 , O₂, CO₂, and waste by-products; metabolite transfer
- Immune cells dispersed provide avenues for antigen detection to causes inflammatory and immune responses
- Present all over the body including the nervous system
 - Meninges, Glial cells, vessel walls



CSF leak in Complex Patients

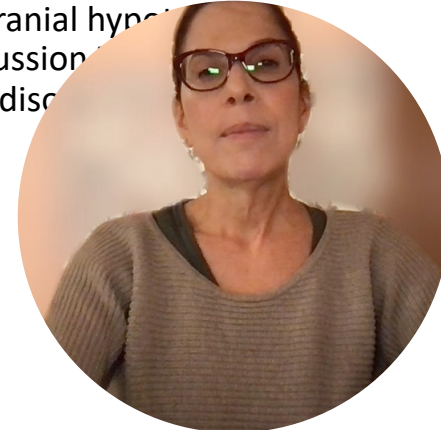
- The dura matter is a fibrous membrane formed by fibrous dense regular connective tissue
 - A little stretched
 - Collagen fibers have indistinct spirality and are densely layered, one above another
 - Composition and architecture of dura can change
 - ` Can weaken

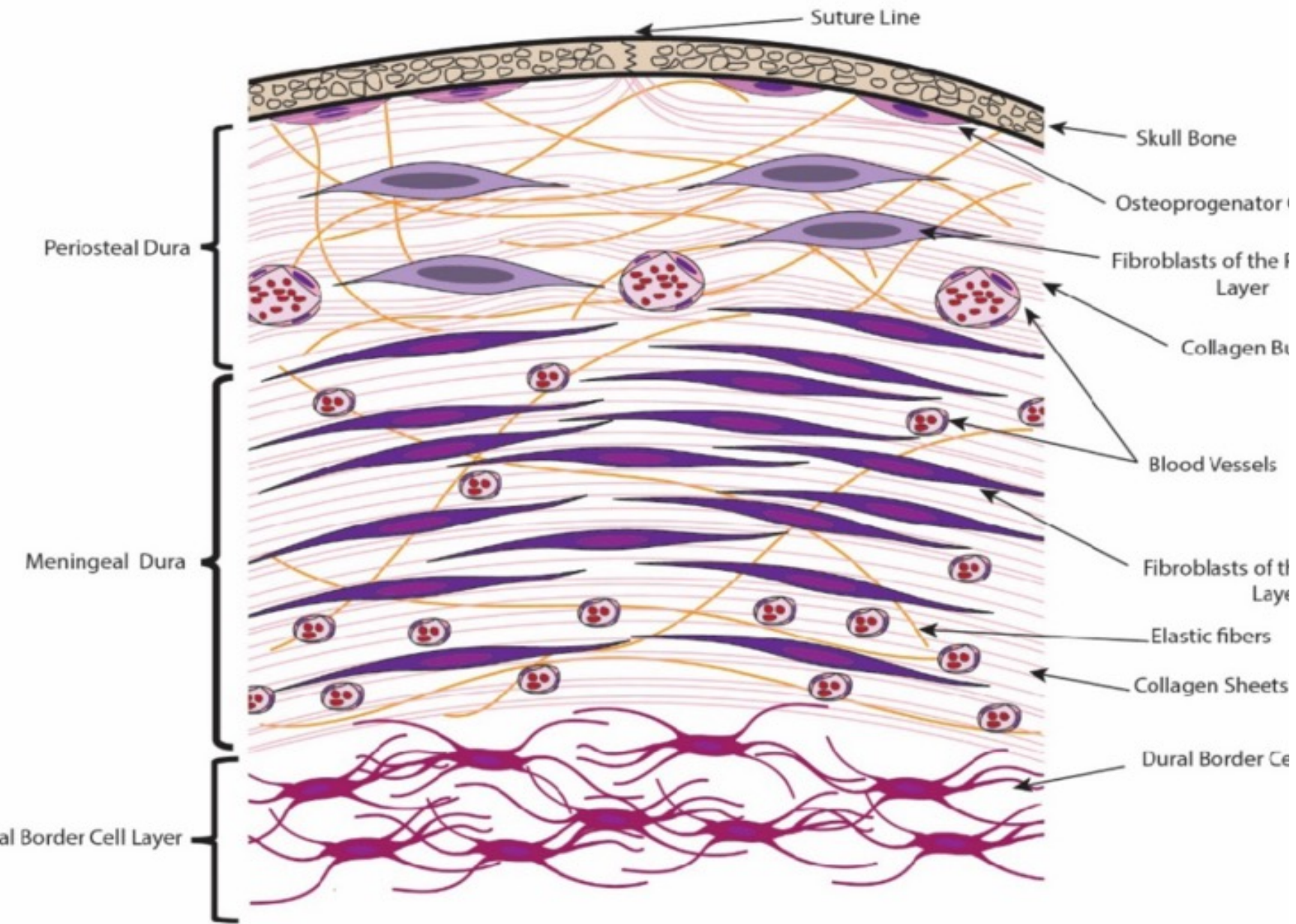


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CSF leak in Complex Patients

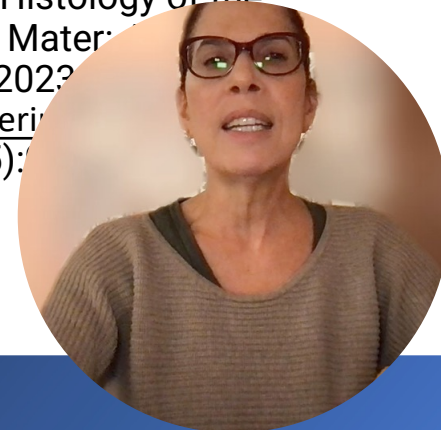
- Extracellular matrix alterations may contribute to loss of dural integrity causing weakness, tear, and meningeal diverticula (Mokri B. Spontaneous Intracranial Hypotension. Continuum (Minneapolis Minn). 2015 Aug;21(4 Headache):1086-108)
- The heterogeneity of connective tissue disease is a challenge for both diagnosis, risk stratification, and research (Schievink WI, Gordon OK, Tourje J. Connective tissue disorders with spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension: a prospective study. Neurosurgery. 2004 Jan;54(1):65-70; discussion 71-2. Maher CO, Sencakova D. Spontaneous CSF leaks: underlying disorders and connective tissue. Neurology. 2002 Mar 12;58(5):814-6.)

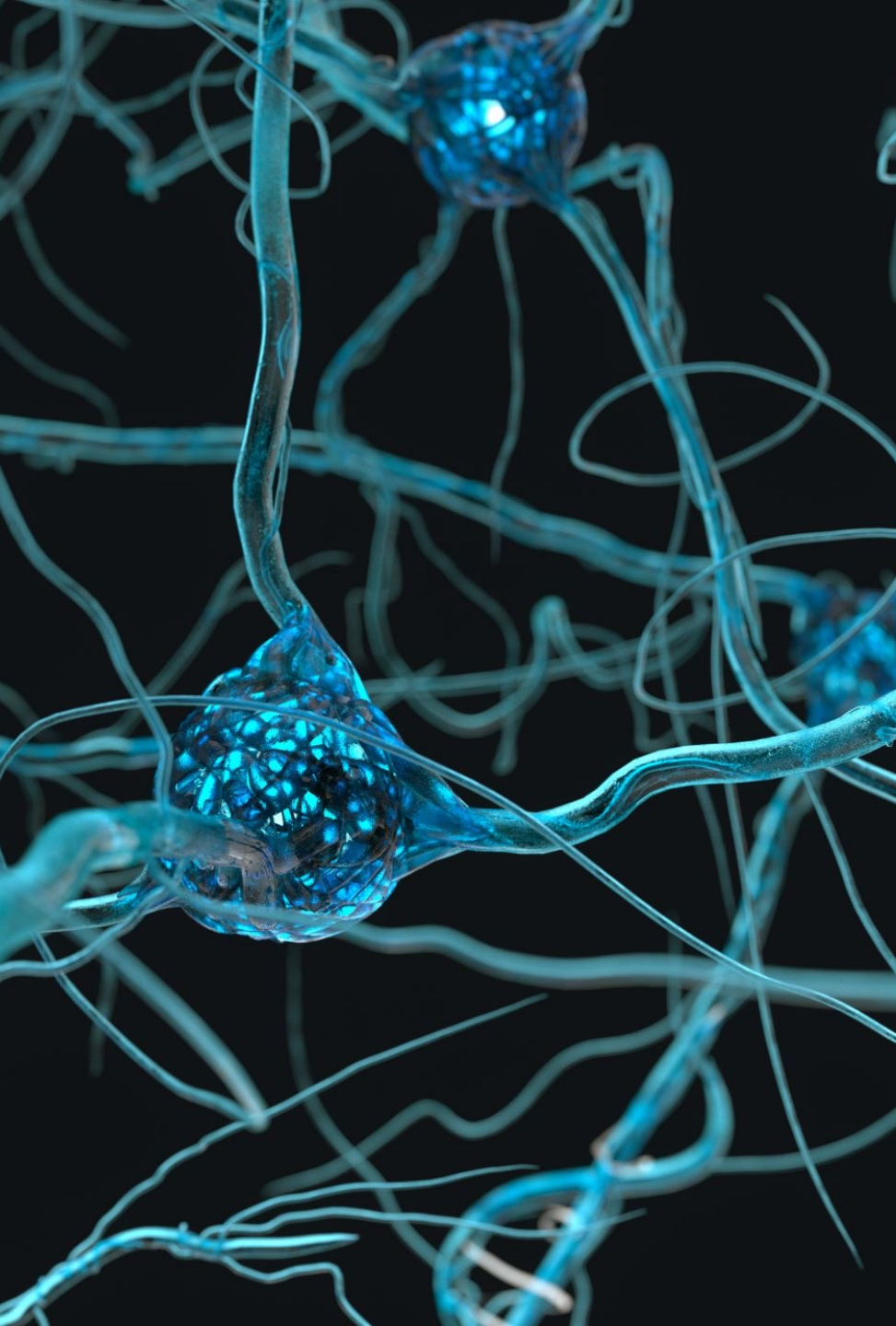




Human Dura Mater

- Hemdan MH. Histology of the Human Dura Mater: A Review Article. July 2023. Journal of Veterinary Medical Sciences 54(5):





Mast Cells

- Sentinel location in tissue: environmental interfaces
 - Dural mast cells
 - Close to nociceptive neurons
 - Release mediators, which initiate a reciprocal communication with specific nociceptors on sensory nerve fibers
 - Dura mater express genes coding for mast cell protease CMA1 and the inflammatory cytokine TNF alpha can occur when under duress from stress, exposure, etc.
(Duque-Wilckens N, Teis R, Sarno E, Stoelting F, Khalid S, Dairi Z, Douma A, Maradiaga N, Hench S, Dharshika CD, Thelen KM, Gulbransen B, Robison AJ, Moeser AJ. Early life adversity drives sex-specific anhedonia and meningeal immune gene expression through mast cell activation. Brain Behav Immun. 2022 Jul;103:73-84.)
 - Mast cells, being near the perivasculature especially within the dura, on the brain side of the BBB strategically located to wreak havoc with the SD. Mast Cell - Glia Dialogue in Chronic Pain and Neuropathic Pain: Barrier Implications. CNS Neurol Disord Drug Targets. 2016;15(1):1-12.



Approach to the Complex Patient

Comprehensive history

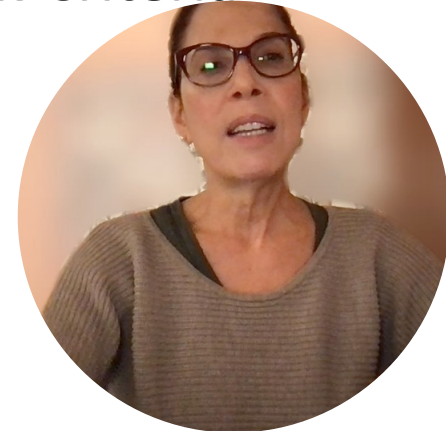
Comprehensive workup

- MCAS evaluation and treatment
 - Not just histamine or tryptase
 - Mast cells have almost 1,000 mediators
 - Proteases that break down collagen fiber types
 - Inflammatory mediators
 - Not just antihistamines
 - Need to stabilize mast cells and counteract other mediators



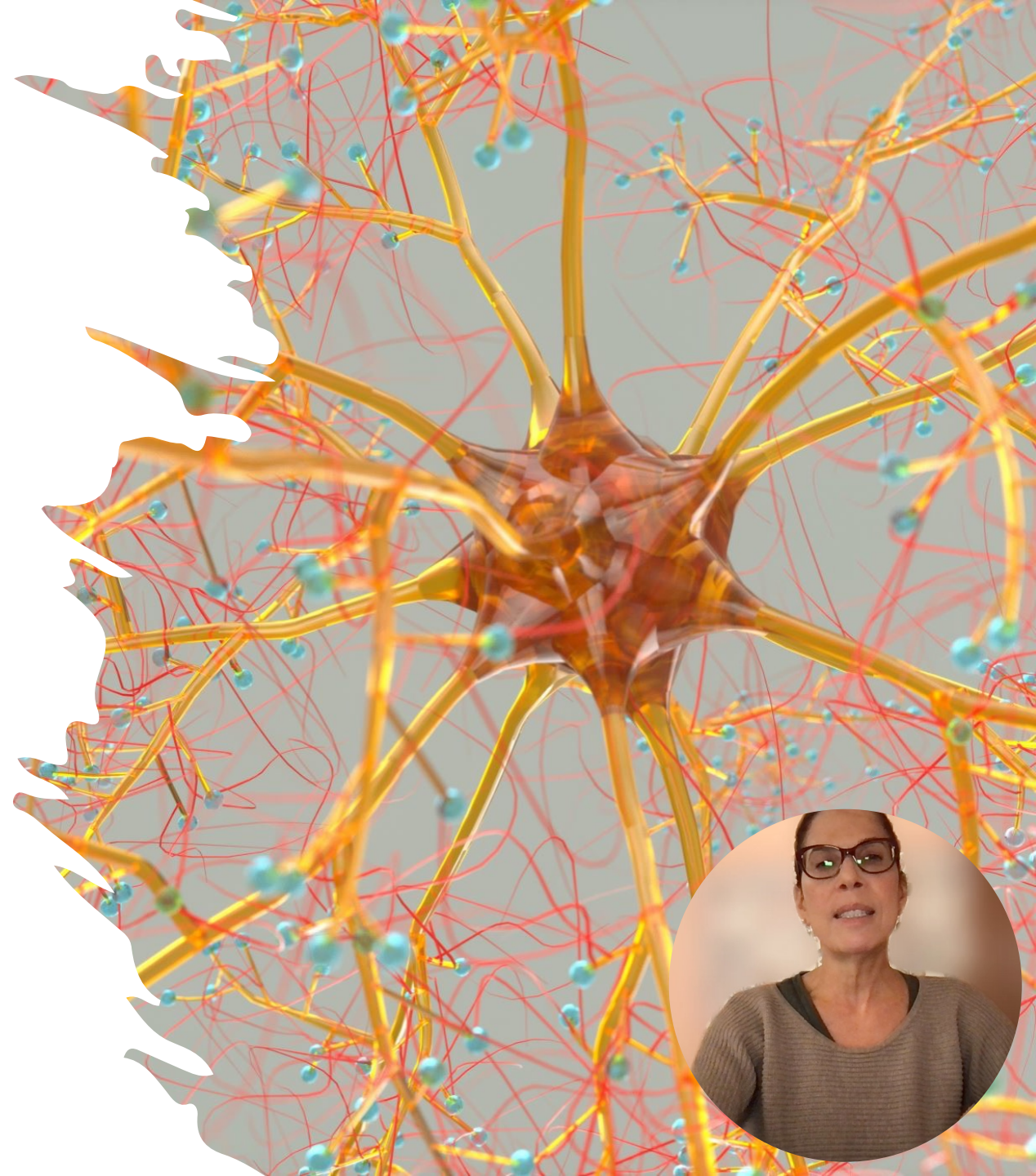
Approach to the Complex Patient

- Patients with suspected dural tears should be evaluated based on criteria set by the International Headache Society, radiological findings, and a differential diagnosis to accurately identify the tear and its potential secondary complications (Gandhi J, DiMatteo A, Joshi G, Smith NL, Khan SA. Cerebrospinal fluid leaks secondary to dural tears: a review of etiology, clinical evaluation, and management. Int J Neurosci. 2021 Jul;131(7):689-695.)
- **Consider evaluating by current hEDS criteria.**
 - **<https://www.ehlers-danlos.com/wp-content/uploads/2017/05/hEDS-Dx-Criteria-checklist-1.pdf>**



The Complex Patient

- Connective tissue is everywhere
 - Joints
 - Vessels
 - Skin
 - Dura
 - Visceral
 - Nerves
- Explains the heterogenous nature of phenotypical presentations
 - Results in many different manifestations
 - Recurrent leak patients
 - “Closed leak” patients with persistent symptoms



Questions?



Thank you

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