

Psychiatric Symptoms Driven by Underlying ME/CFS

Could We Possibly be Missing an Underlying Multisystem Illness?

August 25th, 2020 University of Utah Neuropsychiatic Institute

Brayden Yellman, MD



No Disclosures

(except perhaps a healthy skepticism for ANA testing...)



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Chief Complaint: seizures and increasing diffuse muscular pain

<u>HPI</u>:

- -Had been noting nausea and anorexia earlier in the day, took a nap
- -After the nap, got up to take a shower
- -Nausea, palpitations, facial flushing, anxiety all increased while showering and she ended her shower early after 1-2 minutes
- -Stepped out of the shower, standing in front of the mirror, started to dry her hair
- -Began to experience moderate amplitude "tremors" in both upper extremities and within the neck
- -Became disoriented, somewhat unresponsive to nearby husband
- -Then experienced an episode of syncope, may have "bumped" the side of her head on the edge of the bathroom counter during syncopal episode



HPI (continued):

- -No true loss of consciousness
- -Duration of tremors prior to syncope was about 30 seconds
- -Husband reports 30 minutes of post-ictal confusion, word-finding difficulties, disorientation
- -No preceding aura
- -No loss of bowel or bladder continence
- -No tongue biting
- -No new medications or supplements
- -Denies EtOH, tobacco, illicit drug use





HPI (continued):

-Over past two years, had experienced perhaps ten similar but "milder tremoring episodes" without syncope, though she would usually lie down almost immediately upon symptom onset

-Recent non-febrile upper respiratory illness w rhinorrhea, sinus pain, anterior cervical LAD, cough in setting of known sick contact: daughter

-Stressful home situation due to increasing medical bills for patient's recurrent trips to various medical specialists

-Patient's grandmother recently passed away





<u>PMH</u>:

- Depression
- Chronic Pain/Fibromyalgia
- Generalized Anxiety Disorder
- Chronic Migraines
- Panic Attacks
- ADHD
- Dysmenorrhea
- Interstitial Cystitis
- IBS
- Restless Leg Syndrome
- Eczema
- Raynaud's
- Exercise-Induced Asthma
- Seasonal Allergic Rhinitis

<u>SH</u>:

PSH:

- No tobacco, drugs
- Rare EtOH, feels "sick" after drinking
- Gymnastics when young, but no sports after grade school
- Associates Degree
- Worked at the front desk in a chiropractic office for a few years, currently a homemaker
- 2 children, 1 dog

- Cholecystesctomy
- Left foot Lisfranc fracture s/p ORIF



<u>FH</u>:

- Father Prostate CA
- Mother Chronic Fatigue Syndrome
- Sister Anxiety D/O



Medications:

- Albuterol (prn)
- Bupropion
- Rizatriptan
- Lorazepam (prn panic attack)
- Hyoscyamine
- Lisdexamphetamine
- Kyleena OCP
- Thiamine
- Zinc
- Vitamin D
- Vitamin B12
- Vitamin C
- Ferrous Sulfate
- Arginine
- Probiotics
- Co-Q-10
- Melatonin



<u>Allergies</u>:

- Fluoxetine
- Escitalopram
- Buspirone
- Topiramate
- Alprazolam
- Ciprofloxacin
- Modafinil
- Fluticasone (nasal)
- Perfume
- Lemons
- Baking Soda
- Febreze
- Jell-O
- Paint
- Play-Doh
- Watermelon
- Mites
- Molds
- Band-Aid Adhesive
- Bananas
- Latex





Cardiology:

Vitals: T: 98.6, HR: 107, BP: 102/68, RR: 14, SpO2: 97%

- Normal heart and lung physical exam
- CMP, CBC, ESR, CRP, CPK, troponin, TSH, prolactin all normal
- ANA of 1:80
- Sinus tachycardia on 48-hour Holter monitor
- Normal transthoracic echocardiogram
- Syncope episode not thought to be cardiogenic





<u>Neurologist</u>:

- Tremors not consistent with tonic-clonic movements
- Normal neurological exam in clinic
- MRI of brain unremarkable for masses, demyelinating disease, MTS
- EEG study without epileptiform activity
- No indication for epilepsy video monitoring unit study
- No limitations on driving
- No AED's prescribed
- Asked to consider seeking care from behavioral health





She now presents to your office for assistance...





Pseudoseizure?



Psychogenic Nonepileptic Seizure (PNES)

What can you do for this patient?

- Perform a good psychiatric history with particular focus upon possible co-morbid conditions Most common co-morbid conditions are:
 - a.) Depression
 - b.) Anxiety
 - c.) Somatic Symptom Related Disorders
 - d.) Dissociative Disorders
 - e.) Personality Disorders (borderline, narcissistic, histrionic, antisocial)
- Elect to perform formal neuropsychiatric testing
- Offer a non-judgmental diagnosis





• Consider treatment with cognitive behavioral therapy or other methods of psychotherapy



Depression?

DSM-5 diagnostic criteria for a major depressive episode

A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

NOTE: Do not include symptoms that are clearly attributable to another medical condition.

 Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad, empty, hopeless) or observations made by others (eg, appears tearful). (NOTE: In children and adolescents, can be irritable mood.)

2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation)

3) Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (NOTE: In children, consider failure to make expected weight gain.)

4) Insomnia or hypersomnia nearly every day

5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

Fatigue or loss of energy nearly every day

7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

 Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by their subjective account or as observed by others)

 Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the direct physiological effects of a substance or to another medical condition.





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- A. Excessive anxiety and worry occurring more days than not for at least six months, about a number of events or activities
- B. The individual finds it difficult to control the worry. \checkmark
- C. The anxiety and worry are associated with three (or more) of the following six symptoms:

 - Difficulty concentrating or mind going blank
 - Irritability ✔

 - Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)
- D. Symptoms cause significant distress or impairment in social, occupational, or other functioning 🗸
- E. The disturbance is not attributable to the physiological effects of a substance
 - (eg, a drug of abuse, a medication) or another medical condition (eg, hyperthyroidism) 🗸





Conversion Disorder/Somatoform Disorder?

Subtypes (from most to least common):

- Psychogenic Nonepileptic Seizure 🖌
- <u>Weakness and Paralysis (31%)</u> ٠
 - -May report a history of dropping things, or "dragging" or sudden buckling of the affected leg 🗸
 - -Unilateral, hemiparetic symptoms are most frequent, but weakness in just one limb or in both legs also occurs 🗸
 - -Conversion weakness may be associated with panic attacks, physical injury to the affected limb, or pain 🗸
 - -Must be inconsistent at different times of the examination 🗸

Abnormal Movement ٠

-Psychogenic tremor 🖌 -Psychogenic dystonia 🖌 -Psychogenic gait disorder 🚫 -Psychogenic myoclonus -Psychogenic Parkinsonism 🚫 Stone J, Carson A, Aditya H, et al. The role of physical injury in motor and sensory conversion symptoms: a systematic and narrative review. J Psychosom Res. 2009;66(5):383-390. doi:10.1016/j.jpsychores.2008.07.010

Sharpe M, Walker J, Williams C, et al. Guided self-help for functional (psychogenic) symptoms: a randomized controlled efficacy trial. Neurology. 2011;77(6):564-572. doi:10.1212/WNL.0b013e318228c0c7

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Conversion Disorder/Somatoform Disorder?

Subtypes (from most to least common, cont.):

Speech Symptoms

-Functional dysphonia, often presenting as hoarseness or whispering 🖌 -Other symptoms include intermittent slurred speech, stuttering speech, or telegrammatic speech 🗸 -Confirmed by normal vocal cord movement on laryngoscopy

Globus Sensation •

-Feeling of a "lump" or "ball" in the throat, most often when swallowing 🖌

Sensory Symptoms •

-Paresthesias occur in 50% of cases 🗸 -Numbness occurs in 41% of cases 🖌

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Conversion Disorder/Somatoform Disorder

<u>Subtypes (from most to least common, cont.)</u>:

- Visual Symptoms (16%)
 - -Intermittent blurred vision 🗸
 - -Double vision 🚫
 - -Nystagmus 🗸
 - -Visual Field Defects 🚫
 - -Complete Blindness
- <u>Cognitive Symptoms</u>
 - -Poor concentration and memory 🗸
 - -Impaired Fluency 🗸
 - -Jumbling of Words When Speaking 🖌
 - -Word-Finding Difficulty 🖌
 - -Variability in Speed of Response 🗸



Depersonalization/Derealization (Dissociative Disorder Spectrum)?

Core Symptomatology:

- Unreality of self, defined as feeling detached from one's physical body, mind and thoughts
- Perceptual alterations, which encompasses visual, tactile, and somatosensory distortions
- Emotional numbing, characterized by blunted affect, pain and volition
- Anomalous subjective recall, which consists of disrupted experiences of time and related imagery
- Alienation from surroundings, which comprises symptoms of derealization











Personality Disorders?

Did not meet criteria for borderline, narcissistic, histrionic, or antisocial personality disorders by history or by neuropsychological testing





The Patient's Perspective





The PCP's Perspective





The Behavioral Health Specialist's Perspective





Bateman Horne Center Psychogenic Nonepileptic Seizure (PNES)

Neuropsychological Testing:

- May reveal mild cognitive deficits, especially with attention and working memory
- Frequent failure to recognize words that have been repeated upon multiple occasions but in the ABSENCE of a "negative response bias" (not recalling a word vs recalling a word incorrectly)
- Though many argue these deficits may result from emotional distress, findings of underling depression or anxiety within PNES patients do not differ significantly in incidence from those found in a cohort of patients with left temporal lobe epilepsy
 - Increased use of AED's, neural damage, or something else?
- <u>Minnesota Multiphasic Personality Inventory (MMPI-2)</u> testing is often remarkable for high scoring withing the hypochondriasis and hysteria subscales as well as high somatic complaint scores upon restructured clinical scales (RC1)

Bateman Horne Center Psychogenic Nonepileptic Seizure (PNES)

Risk Factors for Worse Prognosis:

- Social Isolation
- Limited Family Support
- Dependent Lifestyle
- Rejection of PNES Diagnosis
- Chronic Pain Syndromes
- Chronic Migraine and Other Headache Syndromes
- Lower Educational Level
- Unemployment
- Receipt of Social Security Disability Benefits
- Lower Intelligence (measured by IQ)
- Absence of a Formal Treatment Plan
- Longer Duration of Symptoms
- Older Age at Onset



McKenzie P, Oto M, Russell A, Pelosi A, Duncan R. Early outcomes and predictors in 260 patients with psychogenic nonepileptic attacks. *Neurology*. 2010;74(1):64-69. doi:10.1212/WNL.0b013e3181c7da6a





Reuber M, Pukrop R, Bauer J, Helmstaedter C, Tessendorf N, Elger CE. Outcome in psychogenic nonepileptic seizures: 1 to 10-year follow-up in 164 patients. *Ann Neurol*. 2003;53(3):305-311. doi:10.1002/ana.3000

Arain AM, Hamadani AM, Islam S, Abou-Khalil BW. Predictors of early seizure remission after diagnosis of psychogenic nonepileptic seizures. *Epilepsy Behav*. 2007;11(3):409-412. doi:10.1016/j.yebeh.2007.07.017



Psychogenic Nonepileptic Seizure (PNES)

- Small brain functional connectivity studies using functional connectivity density mapping (FCDM) to collect voxel data and map out local and global density of connectivity have suggested disrupted functional connectivity between the following regions:
 - -Frontal Cortex
 - -Sensorimotor Cortex
 - -Cingulate Gyrus
 - -Insula
 - -Occipital Cortex
- This data is thought to support the hypothesis that patients are experiencing alterations to their attention, sensorimotor, and emotional systems and may be suffering a particular manifestation of a dissociative disorder
- Furthermore, decreased connection density within the occipital cortex was found to correlate with duration of known PNES disease activity. This is thought to reflect an adaptation in these patients for long-term hypervigilance and increased response to external stimuli



Ding J, An D, Liao W, et al. Abnormal functional connectivity density in psychogenic non-epileptic seizures. *Epilepsy Res*. 2014;108(7):1184-1194. doi:10.1016/j.eplepsyres.2014.05.006



This Goofy Guy's Perspective....

Something else might be going on here...

And its definitely NOT Lupus!





10-Minute NASA Lean Test





10-Minute NASA Lean Test in our 31 y.o. female

Lying Supine:

Supine 1 minute BP: 108/62 Pulse: 88 Supine 2 minute BP: 108/60 Pulse: 89

PULSE PRESSURE: 48

Standing Upright Leaning Against the Wall:

Standing 0 minute BP:106/64 Pulse: 114 "Lightheaded, weak, chest discomfort"Standing 1 minute BP:104/68 Pulse: 112Standing 2 minute BP:100/72 Pulse: 118 Observers: feet becoming dusky and cyanoticStanding 3 minute BP:102/72 Pulse: 121Standing 4 minute BP:98/70 Pulse: 118 "Nauseated, feeling sick"Standing 5 minute BP:100/74 Pulse: 128 Observers: finger tips becoming dusky and cyanoticStanding 6 minute BP:96/74 Pulse: 126 Observers: Mild rhythmic, "beating" tremor in the neck and RUEStanding 7 minute BP:92/78 Pulse: 132

Test Aborted at this Time Due to Impending Syncope – Patient reported the beating as similar to initial seizure symptoms

HR: 88 \rightarrow 132 (44 bmp increase) Pulse Pressure: 48 \rightarrow 18 (30 mmHg drop)





Sandroni, P., & Low, P. A. (2015). *Autonomic disorders: A case-based approach*. Cambridge: Cambridge University Press.





From Accelerating Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome/NIAID, NIH 2019 Conference: "Orthostatic Intolerance in ME/CFS: Gaps and Gains," by Rowe, PC., Johns Hopkins University School of Medicine, (<u>https://videocast.nih.gov/watch=31640</u>). Aired April 4, 2019. Accessed April 12, 2020. Adapted with written permission granted by Rowe, PC., on June 25th 2020.



- Postural Orthostatic Tachycardia Syndrome (POTS) is identified when there is a >30 bmp HR increase in adults or >40 bmp HR increase in children and adolescents
- The decrease in pulse pressure, primarily mediated by rises in the diastolic blood pressure remains of equal diagnostic value and should not be overlooked
- Critical to understand that POTS is not really a diagnosis itself and instead best represents
 a clinical observation of HR and blood pressure changes upon an orthostatic challenge
- The HR increase and pulse pressure decreases seen on this test are likely more emblematic of compensatory responses to the underlying physiological challenge of being upright aimed at increasing overall cardiac output and cerebral perfusion pressure



10 Minute NASA Lean Test

Must be performed for a full 10 minutes to achieve sensitivity for detection of POTS physiology



Table 3. Proportion of each minute of an abb	POTS diagnoses that would be missed at reviated standing test (full sample, $N = 93$).
Minutes upright	POTS diagnoses missed at each minute
%	(95% CI)
1	70 (60-78)
2	53 (43-63)
3	43 (33–53)
4	37 (27-47)
5	27 (19–37)
6	24 (16-33)
7	15 (9-24)
8	10 (5-17)
9	5 (2-12)
10	0

More sensitive than standard tilt table testing for detecting physiological features of orthostatic intolerance

Maria Roma, Colleen L. Marden & Peter C. Rowe (2018) Passive standing tests for the office diagnosis of postural tachycardia syndrome: New methodological considerations, Fatigue: Biomedicine, Health & Behavior, 6:4, 179 192, DOI: <u>10.1080/21641846.2018.1512836</u>



- A recent study measured total transcranial blood flow with doppler ultrasound upon orthostatic challenge from a tilt table found a 26% decrease in cerebral blood flow in ME/CFS patients as compared to a cerebral blood flow reduction of only 7% in healthy controls.
- Most strikingly, though, was the finding of a 24% cerebral blood flow reduction in those with ME/CFS who did NOT meet criteria for major heart rate or blood pressure changes with this orthostatic challenge
- It is thought that past perfusion studies performed by various imaging modalities have failed to detect these differences because they are performed in the supine and not upright position
- It is also believed that altered cerebral perfusion related to orthostatic challenge as well as other noted clinical aspects of dysautonomia result in many of the neurosensory, neuromotor, and neurocognitive deficits observed in ME/CFS

van Campen CLMC, Verheugt FWA, Rowe PC, Visser FC. Cerebral blood flow is reduced in ME/CFS during headup tilt testing even in the absence of hypotension or tachycardia: A quantitative, controlled study using Doppler echography. *Clin Neurophysiol Pract*. 2020;5:50-58. Published 2020 Feb 8. doi:10.1016/j.cnp.2020.01.003



Inadequate cerebral blood flow has been associated with:

- Lightheadedness
- Blurred Vision
- Diminished Concentration
- Exercise Intolerance
- Fatigue
- Syncope
- Unusual Neurological Symptoms



Further complicating assessment of these clinical findings is the fact that the persistence of symptoms resulting from upright positioning can be prolonged, thus temporally removing the symptoms of orthostatic intolerance from their initial triggering event. In some cases, these symptoms can last for several days after a severe insult.

<u>The resulting catecholamine surge from decreased</u> <u>cerebral blood flow, furthermore, often leads to</u> <u>additional peripheral cardiovascular symptoms including:</u>

- Palpations
- Dyspnea
- Facial Pallor
- Cold Hands and Feet
- Sweating
- Anxiety
- Chest or Abdominal Discomfort
- Tremor
- Nocturia





Validated N-Back task testing has observed pronounced cognitive delays, increase in testing errors, and decrements in memory, concentration, and information processing that directly correlate with the degree of tilt upon formal tilt table testing.



Increasing orthostatic stress impairs neurocognitive functioning in chronic fatigue syndrome with postural tachycardia syndrome Anthony J. Ocon; Zachary R. Messer ; Marvin S. Medow ; Julian M. Stewart



HADS: Anxiety: 5

HADS: Depression: 8 (borderline depression)

ESS (Epworth Sleepiness Scale): 8 (higher than normal daytime sleepiness)

FIQ-R: 69 (severe impairment of function related to FM pain)







RAND-36/SF-36:

Physical functioning:	10	
Role limitations due to physical health:	0	
Vitality/energy/fatigue:	0	
Role limitation due to emotional problems:	100	
Emotional well-being/mental health:	72	
Social functioning:	50	
Pain:	32.5	
General Health:	25	
Each sub-score reports # of possi	ble 100. Low	= Se

vere







Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. Juenger J. Heart. 2002 Mar;87(3):235-41



Multidimensional Fatigue Inventory (MFI) General Fatigue: 19 Physical Fatigue: 18 Reduced Activity: 17 Reduced Motivation: 10 Mental Fatigue: 15

Score Key: 20/20 possible for each domain, higher score indicates more severe impairment.



ME/CFS 2015 CLINICAL DIAGNOSTIC CRITERIA

*Must be moderate-severe and present >50% of time

CORE CRITERIA (required for diagnosis)

- 1.) Impairment of Normal Function Accompanied by Fatigue, >6 months
- 2.) **PEM: Post-Exertional Malaise***
- 3.) Unrefreshing Sleep*
- 4.) Plus at least one of the following:
 - a.) Cognitive Impairment*
 - b.) Orthostatic Intolerance (Autonomic Nervous System Dysregulation)

Additional common but not "CORE" diagnostic features of illness in the ME/CFS population:

Chronic Pain (headache, muscle and joint aches, hyperalgesia, central sensitivity, tingling, burning, etc.)

Immune Dysregulation (allergy, inflammation, immunodeficiency, chemical sensitivities, food intolerances)

Infections or Immune-Mediated Infectious Response (viral or atypical infections, sore throat, tender lymph nodes, low grade fevers, flu-like symptoms)

Neuroendocrine Manifestations (HPA-axis dysregulation, impaired stress response)

Neuroinflammation (glial cell cytokine release, lactate, temperature increases)

Beyond Myalgic Encephalomyelitis: Redefining an Illness. Institute of Medicine. Washington (DC): National Academies Press (US); 2015 Feb 10. ISBN-13: 978-0-309-31689-7ISBN-10: 0-309-31689-8



Common Co-Morbidities in ME/CFS

- Postural Orthostatic Tachycardia Syndrome (POTS), orthostatic hypotension, dysautonomia
- Small Fiber Polyneuropathy (SFPN) and Peripheral Neuropathy
- Amplified Pain Syndromes/Fibromyalgia & Central and Peripheral Pain Sensitization
- Neuroinflammation
- Mast Cell Activation Syndrome (MCAS), Chemical Sensitivities, Food Intolerances, Chronic Idiopathic Urticaria, Seasonal Allergic Rhinitis, & Exercise-Induced Asthma
- Viral Reactivation (VZV, HSV, HHV-6, EBV, CMV)
- Chronic Migraines and other Chronic Headache Syndromes
- Impaired Gastric Motility, Irritable Bowel Syndrome, Small Intestinal Bacterial Overgrowth (SIBO), Celiac Disease
- Chronic Sleep Disorders ("primary" and otherwise)
- Autoimmune Thyroid Disease, Subclinical Hypothyroidism, Euthyroid-Sick Syndrome



Back to our patient's symptoms with this new information...





Depression?

DSM-5 diagnostic criteria for a major depressive episode

A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

NOTE: Do not include symptoms that are clearly attributable to another medical condition.

 Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad, empty, hopeless) or observations made by others (eg, appears tearful). (NOTE: In children and adolescents, can be irritable mood.)

2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation)

3) Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (NOTE: In children, consider failure to make expected weight gain.)

4) Insomnia or hypersomnia nearly every day

5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

Fatigue or loss of energy nearly every day

7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

 Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by their subjective account or as observed by others)

 Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the direct physiological effects of a substance or to another medical condition.





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- A. Excessive anxiety and worry occurring more days than not for at least six months, about a number of events or activities
- B. The individual finds it difficult to control the worry. \checkmark
- C. The anxiety and worry are associated with three (or more) of the following six symptoms:

 - Difficulty concentrating or mind going blank
 - Irritability ✔

 - Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep) -
- D. Symptoms cause significant distress or impairment in social, occupational, or other functioning 🛹
- E. The disturbance is not attributable to the physiological effects of a substance
 - (eg, a drug of abuse, a medication) or another medical condition (eg, hyperthyroidism) ✔







Conversion Disorder/Somatoform Disorder?

Subtypes (from most to least common):

- Psychogenic Nonepileptic Seizure 🖌
- <u>Weakness and Paralysis (31%)</u> ٠
 - -May report a history of dropping things, or "dragging" or sudden buckling of the affected leg 🗸
 - -Unilateral, hemiparetic symptoms are most frequent, but weakness in just one limb or in both legs also occurs 🗸
 - -Conversion weakness may be associated with panic attacks, physical injury to the affected limb, or pain 🗸
 - -Must be inconsistent at different times of the examination 🗸

Abnormal Movement ٠

-Psychogenic tremor 🖌 -Psychogenic dystonia 🖌 -Psychogenic gait disorder 🚫 -Psychogenic myoclonus -Psychogenic Parkinsonism 🚫 Stone J, Carson A, Aditya H, et al. The role of physical injury in motor and sensory conversion symptoms: a systematic and narrative review. J Psychosom Res. 2009;66(5):383-390. doi:10.1016/j.jpsychores.2008.07.010

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Conversion Disorder/Somatoform Disorder?

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-Functional dysphonia, often presenting as hoarseness or whispering 🖌 -Other symptoms include intermittent slurred speech, stuttering speech, or telegrammatic speech 🗸 -Confirmed by normal vocal cord movement on laryngoscopy

Globus Sensation •

-Feeling of a "lump" or "ball" in the throat, most often when swallowing 🖌

Sensory Symptoms •

-Paresthesias occur in 50% of cases 🗸 -Numbness occurs in 41% of cases 🖌

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Conversion Disorder/Somatoform Disorder

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 - -Intermittent blurred vision 🗸
 - -Double vision 🚫
 - -Nystagmus 🗸
 - -Visual Field Defects 🚫
 - -Complete Blindness
- <u>Cognitive Symptoms</u>
 - -Poor concentration and memory 🗸
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 - -Jumbling of Words When Speaking 🖌
 - -Word-Finding Difficulty 🖌
 - -Variability in Speed of Response 🗸



Conversion Disorder/Somatoform Disorder



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JoloDate



Depersonalization/Derealization (Dissociative Disorder Spectrum)?

Core Symptomatology:

- Unreality of self, defined as feeling detached from one's physical body, mind and thoughts
- Perceptual alterations, which encompasses visual, tactile, and somatosensory distortions
- Emotional numbing, characterized by blunted affect, pain and volition
- Anomalous subjective recall, which consists of disrupted experiences of time and related imagery
- Alienation from surroundings, which comprises symptoms of derealization



Simeon D, Kozin DS, Segal K, Lerch B, Dujour R, Giesbrecht T. De-constructing depersonalization: further evidence for symptom clusters. *Psychiatry Res*. 2008;157(1-3):303-306. doi:10.1016/j.psychres.2007.07.007











Didn't Our Patient Also Have Raynaud's in Her Past Medical History?

Wasn't Her ANA 1:80?

Maybe She Really Does Have Lupus !







-Macular, no texture, blanches to touch, warm to touch
-Margins are gradual, not well-demarcated
-Painful, but not pruritic
-No fevers
-No leukocytosis
-Repeat ANA 1:80
-No improvement with a course of antibiotics
-Could this be autoimmune?





Skin Biopsy:

- -No particular neutrophilic or lymphocytic infiltration recognized
- -No interface dermatitis or positive immunofluorescent stains
- -No infectious organisms identified
- -Decreased innervation of the skin by small fiber nerves



- 40% of fibromyalgia patients will have skin biopsies positive for SFPN
- SFPN is not merely associated with pain syndromes, but is often a cause of (or result of) underlying systemic illnesses



- Estimated that 90% of cases of SFPN are undiagnosed and untreated
- Some estimates suggest a worldwide prevalence of 400-500 million people suffering with small fiber neuropathy





EMG/NCS and formal neurologic exams are not sensitive for the detection of small fiber polyneuropathy



Small Fiber Polyneuropathy (SFPN)

Gold-standard for diagnosis is a 3 mm punch biopsy of the lower leg, as all epidermal nerve fibers are small fibers



Oaklander AL, Nolano M. Scientific Advances in and Clinical Approaches to Small-Fiber Polyneuropathy: A Review. JAMA Neurol. 2019;76(10):1240–1251. doi:10.1001/jamaneurol.2019.2917





"Small-fibers" include different types of nerve cells

- A-delta fibers
- autonomic axons

Small Fiber Nerves:

- Small unmyelinated sensory
 afferent C-fibers
- Thinly myelinated A-delta fibers
- Post-ganglionic, sympathetic autonomic axons

These nerves are small diameter fibers that innervate most organs and tissues



Sensory Pain and itch innervation of skin

Vasomotor innervation of arteriovenous anastamosis

Sudomotor innervation of sweat gland

Pilomotor innervation of arrector pili muscles





Loss of axon innervation of myovascular structures in small fiber neuropathies

Dori, A., Lopate, G., Keeling, R. and Pestronk, A. (2015), Myovascular innervation: Axon loss in small-fiber neuropathies. Muscle Nerve, 51: 514-521. doi:10.1002/mus.24356





- Loss of myovascular innervation can result in vessel patency that leads to arteriovenous shunting of blood
- Capillary beds can be entirely bypassed in this distal "left to right" shunt



Phillip J. Albrecht, PhD, Quanzhi Hou, MD PhD, Charles E. Argoff, MD, James R. Storey, MD, James P. Wymer, MD PhD, Frank L. Rice, PhD, Excessive Peptidergic Sensory Innervation of Cutaneous Arteriole– Venule Shunts (AVS) in the Palmar Glabrous Skin of Fibromyalgia Patients: Implications for Widespread Deep Tissue Pain and Fatigue, *Pain Medicine*, Volume 14, Issue 6, June 2013, Pages 895–915



Autonomic Functions of Small Fiber Nerves:

- Heart rate response to deep breathing
- Heart rate and blood pressure response to Valsalva
- Heart rate and blood pressure response to tilt
- Sudomotor (sweat) response
- Gastrointestinal functions





The gut is densely innervated by small fibers as well, and loss of these fibers can result in wide ranging abdominal and digestive symptoms including:

GI Symptoms of SFPN:

- GI Dysmotility
 - Esophageal Dysmotility
 - Gastric-emptying scintigraphs shows
 slowed emptying of the stomach
 - Sitz marker studies show alterations of colon transit time
- Post-prandial nausea and vomiting
- GERD
- Weight Loss/Anorexia/Cachexia
- Diarrhea
- Constipation
- Irritable Bowel Syndrome (IBS)









- Taught to "pace" activity, remain within her metabolic energy limits, and to avoid pushing herself into the clearly injurious state of post-exertional malaise
- Husband helps do more of the chores around the house to keep her from exceeding her "energy envelope"
- Treated for orthostatic intolerance with increased fluid and sodium administration, compression clothing, fludrocortisone, pyridostigmine, midodrine
- Treated for FM, SFPN, neuroinflammation with Low Dose Naltrexone
- Treated for neurological and sensory hypervigilance as well as disrupted sleep with vivid dreams and increased startle response with clonidine at night
- Migraines are reduced in both intensity and duration with use of a CGRP antagonist
- Gabapentin before bed helps initiate sleep and decrease RLS symptoms
- Uses lorazepam prn for "panic attacks" which appear to be related to exertional or positional exertion driving a peripheral sympathetic response
- Did not require pharmacotherapy for symptoms of depression in the setting of the above treatments
- Awarded social security disability
- Clinically no longer experiencing symptoms of PNES, tolerates approximately 4 hours of upright activity (sitting or standing with feet on the floor) per day, brain fog and cognitive symptoms are reportedly and measuredly improved, sleep feels refreshing and restorative, and pain scores are reduced to an average of 4/10 daily





Questions?



