

# Post-Viral Syndromes: Who's in the driver's seat?

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Session 1



<https://physicians.utah.edu/echo/long-covid>

<https://batemanhornecenter.org/providers/long-covid/project-echo/#long-covid-post-viral>



Patient cases are shared in this session for educational purposes. In some cases, the information does not relate to an individual, and instead represents a compilation of disease presentation.

In cases involving individual patient information, the patients have authorized the discussion of their case in this setting.

# Objectives and Scope

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# Case 1: Hypertensive Urgency and Psychogenic Non-Epileptic Seizure

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# History of Present Illness

49 y.o. female presented for evaluation of significant fatigue, seizure episodes, hypertensive urgency, and concern for ME/CFS

- Fatigue beginning gradually in 2015 but became functionally impaired after planning a large extended family reunion in 2016 from which she never recovered
- Fatigue accompanied by upright activity intolerance and gradual inability to walk more than a few steps within a room without needing to sit due to impending weakness vs syncope → ended up in a motorized wheelchair
- Neurological workup to date had been unremarkable for any neurological or neuromuscular pathology

# History of Present Illness

22 “Good Days” per month with 4 hours of upright activity

- Can: read, sew, crochet, use a computer, have a conversation, dress herself, eat
- Cannot: stand for >2-3 minutes, walk more than a few steps, shower w/out help

8 “Bad Days” per month with <1 hour of upright activity

- Can: listen to audio books, watch videos, eat, use the restroom
- Cannot: read, prepare a meal, dress, bathe, use hands for fine motor movements, perform other activities out of bed

# History of Present Illness

- Difficulty falling asleep, often feeling excessively “wired” when most exhausted
- Sleep also fragmented with frequent awakening, often with vivid stressful dreams or frank nightmares
  
- Diffuse upper and lower abdominal pain, generally after eating
- Associated early satiety, bloating, belching, nausea without emesis, constipation
- Abdominal pain immediately exacerbated after taking medications of many pharmacological classes
- General diffuse tenderness over the abdominal wall → could not wear tight clothing or high-waisted pants

# History of Present Illness

- Would frequently present to medical offices with “hypertensive urgency” with blood pressures in the 190’s/130’s
- Patient would measure blood pressures at home (supine) and record average blood pressures in the 150/90 range → patient argued she had “severe white coat syndrome”
- No hx of stroke, TIA, related headaches, or related vision changes
- Unable to tolerate various antihypertensives due to abdominal discomfort, lightheadedness/dizziness, or increasing fatigue/weakness



# Seizure “Episodes/Spells”

- Beginning October 2017
- Begins shaking and trembling without true “tonic-clonic” movements
- No tongue biting, urinary incontinence
- Unresponsive during episodes, but can remember events and feel pain after a short “post-ictal” confusion and recovery period
- Duration from several minutes up 6 hours, most often about an hour in duration
- Most frequently occurring when patient very fatigued, worn out, exhausted, stressed
- Occur often at night when going to or returning from the restroom
- Observed in an epilepsy monitoring unit for 2.5 days without EEG evidence for epileptiform activity
- No improvement after a trial of CBT, but difficult to concentrate on therapy
- Still occurring daily, sometimes several episodes per day

# Past Medical History

- Left Ventricular Hypertrophy
- Hypertensive Urgency/HTN
- Psychogenic Nonepileptic Seizure
- Romano Ward Syndrome (prolonged QT) with Frequent PVC's s/p Cardiac Ablation
- Chronic Abdominal Pain/IBS
- Conversion Disorder/PNES
- Recurrent HSV labialis
- Generalized Anxiety Disorder
- OSA (mild on CPAP)
- Hyperlipidemia
- Hx of cholecystectomy and appendectomy

# Medications

- Cyanocobalamin IM
- Diphenhydramine 12.5 mg po bid
- Acetaminophen 650 mg po bid

## Recently Unable to Tolerate:

- Lisinopril (abd pain)
- Amlodipine (fatigue, weakness)
- Verapamil (palpitations, dizzy)
- Tramadol (abd pain)
- Promethazine (abd pain)
- Amitriptyline (fatigue, abd pain)
- Sertraline (worsened mood)

Orthostatic Hypotension Questionnaire (OHQ): 34/60  
Orthostatic Hypotension Daily Activity Scale (OHDAS): 39/40  
Orthostatic Intolerance Questionnaires Total Score: 73/100

## Hospital Anxiety and Depression Scale:

AS: 6, DS: 4 (0-7 nml, 8-10 borderline, 11-21 abnormal)

## RAND-36/SF-36:

Physical Functioning: 5

Role Limitations Due To Physical Health: 0

Bodily Pain: 45

General Health: 10

Vitality/Energy/Fatigue: 15

Social Functioning: 25

Role Limitation Due to Emotional Problems: 100

Emotional Well-Being/Mental Health: 92

Scores on a scale of 100/100

Lower score equals more severe impairment

# PHYSICAL EXAM

**Vitals:** AF, Pulse: 104, BP: 200/140, RR: 16, SpO2: 97%

**Gen:** A&Ox3, NAD, sitting in a motorized wheelchair

**HEENT:** PERRL; EOM intact; **dilated bilateral pupils in dark room**; normal TM's; normal oropharynx; normal dentition

**Neck:** no LAD; nml thyroid; no carotid bruits

**CV:** **tachycardic** with regular rhythm; no m/r/g/clicks; normal distal pulses

**Pulm:** CTAB; no wheezes, rales, rhonchi

**GI:** soft; **diffuse tenderness to light palpation**; no masses, no HSM, normal bowel sounds

**Ext:** 2+ pitting edema to the mid-tibia's bilaterally; **delayed 4 second capillary refill in the bilateral distal toes and 2 second delayed capillary refill in the bilateral distal fingers**

**Skin:** no rashes; hands and feet cool to touch; feet dusky to the ankles

**MSK:** **17/18 FM tender points positive**; Beighton 2/9 (elbows);

**Neuro:** strength 5/5 throughout proximal/distal musculature; DTR's 2+ and symmetric throughout; **absent vibratory sense in the bilateral 5<sup>th</sup> digits of the lower extremities**; normal cerebellar reflexes; negative Hoffman's sign

# 10-Minute Standing (NASA Lean) Testing

## Lying Supine:

Supine 1 minute BP:	200/140	Pulse: 96	PP: 60
Supine 2 minute BP:	200/142	Pulse: 95	PP: 59



## Standing Upright Leaning Against the Wall:

Standing 1 minute BP:	200/160	Pulse: 134	PP: 40	Fingers becoming cyanotic. Feet cold and cyanotic.
Standing 2 minute BP:	200/160	Pulse: 112	PP: 40	Right arm “beating.” Both legs shaking. “Light-headed.”
Standing 3 minute BP:	200/164	Pulse: 118	PP: 36	Noble cyanosis of hands and feet. Full body shaking/trembling
Standing 4 minute BP:	206/158	Pulse: 121	PP: 48	“Feeling weak, cannot stand much longer”
Standing 5 minute BP:	206/150	Pulse: 118	PP: 56	Unable to continue, assisted collapse to the floor.

**Test Aborted** – During test felt similar to prodrome before “seizure” events, but impending syncope/weakness interrupted its normal procession of symptoms

# Laboratory Data

WBC: 6.1 (nml diff)

Hgb/Hct; 15.2/46.2

Platelets: 329

Sodium: 141

Potassium: 4.3

Calcium: 9.6

Creatinine: 0.79

ALT: 28

AST: 24

TSH: 0.65

Free T4: 1.1

Vitamin B12: 445

Methylmalonic Acid: 178

Ferritin: 31

Iron: 62

Iron Sat: 18%

Renin: normal

Erythropoietin: 12.8

Jak2 Exon Mutations: negative

ESR: 2

CRP: <0.3

CPK: 45

ANCA: negative

EBV antibodies: negative

HIV: negative

Lyme: negative

Pheochromocytoma: negative

ACTH: 31

Cortisol: 22.5

Tryptase: 3.0 (nml)

# Imaging/Procedural Workup

- **MRI Brain** – chronic small vessel ischemic change of the supratentorial white matter; no acute or chronic infarct
- **EMG/NCS of the Lower Extremities** – normal study without evidence of peripheral neuropathy or myopathy
- **CTA Abd/Pelvis** – no renal artery stenosis; s/p cholecystectomy
- **MR Enterography** – normal small bowel and colon; no stricture, fistula, obstruction, or mass
- **EGD/Colonoscopy/Capsule Endoscopy** – normal esophagus, stomach, small bowel, and colon save for scattered colonic diverticula



# Imaging/Procedural Workup

- **TTE** - mild-to-moderate concentric LVH; EF: 54%; mild LAE; no valvular disease; normal aorta; no pericardial effusion
- **CTA Chest** – normal; no dissection, aneurysm, or sign of coarctation of aorta
- **Autonomic Reflex Study** – blood pressure response to tilt showed hypertension; QSART responses normal; HR response to deep breathing/Valsalva could not be interpreted due to irregular HR
- **Cardiac Electrophysiology Lab** - MV anterolateral pVC; normal SA and AV node functions/ s/ RF ablation for frequent PVC morphology with RBBB

# Found to meet 2015 IOM Criteria for **ME/CFS** with:

- Functional impairment >6 months and associated fatigue
- Post-exertional malaise (PEM)
- Unrefreshing sleep
- Cognitive dysfunction, waxing and waning with brain fog and attentional deficits
- Orthostatic intolerance (POTS, orthostatic hypertension)

# Initial Interventions

## Decrease Sympathetic Response to Physiological Stressors/Reduce Blood Pressure:

- Started 0.1 mg of **clonidine** po bid (alpha blocker for sympathetic dampening)

## Begin to Gradually Treat Orthostatic Intolerance and Observe Vital Signs:

- Begin wearing **compression clothing** (tolerated everywhere but her abdomen)
- Increase oral free water intake, gradually increase sodium via electrolyte packets of liquid IV
- Start ½ tablet of 60 mg **pyridostigmine** every four hours x3 doses daily, then titrated upward to 60 mg three times daily

# Initial Clinical Response

- Easier to fall asleep and stay asleep; not having vivid dreams or nightmares
- Reduction in incidence of “spells” (only 4 in four weeks after all interventions instituted)
- Duration of “spells” reduced to 20 minutes from an hour, recovering quicker with minimal “post-ictal” confusion after “spell” was over
- Function improving → doing lots of crochet projects from bed, getting up ambulating around the bedroom, ambulating to dinner more frequently
- Blood pressure remained at 192/136 in office, but reported much lower blood pressures at home (130’s/80’s upright instead of supine)
- Abdominal pain did not increase with initial interventions

# Clinical Setback

- Caught an infectious gastroenteritis from her husband and son that led to significant nausea and vomiting as well as increasing abdominal cramping and pain
- Unable to keep up with oral fluid and sodium intake, could not take medications orally
- Notable clinical setbacks as well with significant fatigue and weakness (could not leave bed except for trips to the bathroom) as well as frequent seizure “spells”
- Blood pressures at home was 194/126

# Gastroenteritis Response

## Intervention:

- Given 1.5L of **IV normal saline** through home health three days in a row

## Clinical Response:

- Weakness, fatigue, abdominal pain all improved immediately upon fluid repletion
- **Blood pressure modestly decreased with fluids**, and then further when she was able to reintroduce oral clonidine and pyridostigmine

# Further Clinical Strategy

## Further Decrease Sympathetic Response to Physiological Stressors:

- Increased **clonidine** to 0.2 mg po daily, 0.3 mg po qHS
- Added 20 mg of **propranolol** po qHS

## More Aggressive Management of Orthostatic Intolerance:

- Added 0.1 mg of **fludrocortisone**
- Increased **pyridostigmine** to 120 mg po tid (mild loose stools)
- Increased **sodium** dose with free water and electrolyte intake

# Continued Clinical Response

- Only two “seizure spells” over the next 6 weeks, both <10 minutes duration
- Able to walk around her house without her wheelchair, only using wheelchair when leaving her home
- Blood pressure in office of 130/78!!!
- Post-prandial abdominal pain and cramping somewhat improved

However...

- Increasing swelling with pain and redness in the bilateral feet > hands
  - Increasing peripheral edema from fluids, fludrocortisone?



# Further Clinical Interventions

## More Aggressive Management of Orthostatic Intolerance:

- Began 2.5 mg of **midodrine** po tid increased to 5 mg po tid for both management of orthostatic intolerance and for treatment of **erythromelalgia** in the extremities

## Further Decrease Sympathetic Response to Physiological Stressors:

- Began working with the “**dynamic neural retraining system,**” (**DNRS**) which teaches exercises that appear to assist with exerting some conscious control over autonomic nervous system sympathetic responses
- Started 0.5 mg of **aripiprazole** to attempt to decrease sensory sensitivities (light sensitivity, sound sensitivity, feeling overwhelmed in large groups), which otherwise would trigger sympathetic symptoms

# Clinical Improvement

- Reduction in episodes of pain, swelling, redness, and warmth in the distal extremities
- Blood pressure of 133/83 in office
- Not a single “seizure episode” for the subsequent three months
- Only using her motorized wheelchair when leaving the house, but would ambulate around church as well as her own home, unassisted
- Significantly reduced post-prandial abdominal pain, as well as reduced early satiety, bloating, and nausea

Psychogenic non-epileptic seizures may be related to inadequate cerebral perfusion in the context of uncontrolled dysautonomia!

Uncontrolled dysautonomia can lead to profound sympathetic hypertensive responses that actually improve with the same treatments used for orthostatic hypotension!

# Case 2: Anxiety

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# No Disclosures

20-year-old male presented to our clinic 2/1/2023.

**CC:** Worsening chronic fatigue, brain fog, anxiety and insomnia, and concerns about medications. No longer able to live on his own. Hard to hold down a job.

**Initial infection** - November 2019. Was age 18 and in senior year of HS.

- Fatigue, n/v, chest and nasal congestion, SOB, chest tightness, and b/a. Denied loss of taste or smell. Sick for 4-5 days and back to normal in a week. Entire workplace was sick with similar symptoms.
- 2-3 weeks later fatigue returned, new onset insomnia, and increasing panic attacks, particularly with driving. Often wakened at night with a panic attack and HR 180bpm, per smart watch.
- Summer 2020 decrease in physical and cognitive stamina, worsened fatigue and anxiety. These symptoms persisted worsened over the next 3 yrs.
- No known COVID infection. Was vaccinated with Pfizer Bivalent vaccine June/July 2022.

## PMH

- ADHD – diagnosed in grade school
- Anxiety/depression – symptoms intermittent and treated with periodic fluoxetine. Took lorazepam a few times a year.
- Environmental allergies
- GERD – intermittent and food related

## Medications at initial visit

- Fluoxetine 20mg QD
- Zolpidem 10mg QHS
- Lorazepam 1mg, 1-2x/day
- Melatonin – marginally helpful

\* pt very concerned about zolpidem and lorazepam dependence

**PE:**  
 -Pt had pupillary dilation, anxious, and sweaty during the entire visit.  
 -HR >130 sitting for exam

**Seated Vitals**  
 BP 130/98 mmHg  
 HR 105 bpm

	SBP	DBP	HR	SBP-DBP/SBP & Symptoms
Supine 1 minute	124	80	101	
Supine 2 minute	122	82	101	35%
Standing 1 minute	138	100	111	28% -pupils dilated, mottled feet, moist hands
Standing 2 minute	148	110	121	26% - mottled hands, very tired
Standing 3 minute	150	112	116	25% - hand numb and mottled
Standing 4 minute	138	120	126	13%- cold to forearms, feet blue
Standing 5 minute	144	118	130	18% - Legs getting sore, shaking
Standing 6 minute	140	120	132	14% - sound sensitivity, dizzy
Standing 7 minute	UNH	UNH	134	Shaking, mottled hands and feet
Standing 8 minute				<b>TEST STOPPED</b>
▲	↑ 28	↑ 40	↑ 33*	*HR of $\geq 30$ bpm or >120 bpm is required for POTS diagnosis in adults *PP/SBP < 25% is pathologic



## Diagnostic findings from initial visit – 02/07/2023

### CBC

- RBCs 5.98 (H)
- HgB 18.5 (H)
- MPV 8.3 (L)
- Hematocrit nl
- All other indices normal

### CMP

- Calcium 11.1 (H)
- ALT 56 (H)
- AST 27
- All other indices normal

Vitamin D 28, (L)

Histamine 43 (H)

IgE 172 (H), <100

Tryptase 3.4

### EBV Panel

- IgM and Early Antigen neg
- IgG Anti VCA 6.7 (H)
- IgG NA (H) >8.0

Vitamin B12 668

CRP 0.2

ESR 2.0

ACTH 60.2

Cortisol (12:30pm) 20.2

TSH 2.32

Free T4 0.97

HgB A1c – 4.6

HIV - negative

RPR - negative

Urinalysis – negative

### Immunoglobulin Panel

- IgA 290
- IgG 1240
- IgM 125

### Other diagnostics

- Normal Echocardiogram
- PSG- AHI 6.8, no CSA

### Prior pertinent labs 7/17/2022

- CK 52
- ANA IFA screen negative

### F/u labs 3 months later

- CMP
- --Calcium 10.6 (H) 10.4nl
- --ALT 52 (N)
- PTH 42 (N)
- Vitamin D 39 with supp

# Diagnoses from first visit

- **Post Viral Fatigue Syndrome** - met 2015 IOM criteria for ME/CFS  
Viral trigger unknown - maybe Influenza, EBV, a little early for SARS CoV2
- **Dysautonomia with POTS** - HR >120 on NLT, venous pooling, premature A/V shunting, venous pooling, s&s of Sympathetic Over Drive (SOD) – pupillary dilation, sweating, tremors
- **Anxiety and Insomnia** – high suspicion that dysautonomia is the driver of his anxiety
- **Cognitive impairment** – ? Poor perfusion to the brain secondary to decreased cardiac output with standing and possible neuroinflammation.
  
- Mild OSA
- ADHD
- Allergic disorder – elevated IgE, plasma histamine
- Hypercalcemia
- Vitamin D deficiency

# Interventions

## Phase One - Primary target was Dysautonomia

### Increase Vascular Volume!

- 3-4 liters water and with 1 gm sodium/liter – Improved fatigue and brain fog. Reduced anxiety.
- Course of IV NS 1 Liter QOD x 2 wks – Improved anxiety and upright tolerance and created a bridge to initiate therapies.

### Beta Blocker and Alpha blockers

- **Propranolol** 10mg TID - Lowered HR, stabilized BP, improved sleep somewhat, anxiety and insomnia better but not good enough.
- Started **Clonidine** 0.1mg QHS - Questionable benefit at first but then became a staple.
- Compression clothing - Improved upright tolerance and reduced standing HR.
- Pacing and PEM avoidance.

### Biggest changes

- Improved physical stamina and fatigue
- Improving anxiety and insomnia
- Decreased tachycardia
- Improving cognition

## Phase Two

### Pharmacological interventions

- Change to **Propranolol XR** 60mg QHS for better nighttime coverage - am grogginess and worsened brain fog. Changed back to **Propranolol IR** 10mg TID.
- Continued **Clonidine 0.1mg** – recently moved to a patch for 24 hr coverage.
- Initiated **Dextromethorphan** 15mg BID – decrease SOD and increase PEM resilience.
- Started **low dose Aripiprazole** 2 mg for cognition – Improved anxiety and cognition. Improved sleep.
- Using **Hydroxyzine 25-50mg** for sleep and to help reduce the lorazepam at night.

### Non-Pharmacological interventions

- Continued hydration and sodium 3L H2O and 3 gm sodium/day
- Utilizing IV NS therapy as needed for PEM
- Continued compression clothing
- Pacing and PEM avoidance

## Anxiety and Insomnia Management

- Control SOD with correcting POTS by expanding vascular volume, compression clothing, clonidine and prn propranolol.
- Reduce anxiety and insomnia with correcting POTS and utilizing hydroxyzine at night for anxiety and sleep.

## Controlled-Substance Outcomes

- Stopped Zolpidem by July – reducing SOD greatly reduced anxiety symptoms reducing insomnia
- Off Lorazepam x 1 week after slow 2 month wean and utilizing Hydroxyzine 25-50mg at night.

## Functional Outcomes

- Able to sit up all day and work at his computer. Feels he could work FT from home, now that cognition is much better.
- Able to drive for 30 minutes and do low impact errands.
- Able to go bowling and tolerate environments with a lot of stimulation.
- Referring to PT for careful reconditioning to not exacerbate his PEM.

# Case 3 Vignette : Uncontrolled Mast Cell Activation Syndrome

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Brayden Yellman, MD

# History of Present Illness

33 y.o. female with ME/CFS, hEDS, POTS/OI by 10-Minute NASA Lean Test, SFPN, ADHD, and MCAS (serum tryptase elevated) presenting to a follow-up clinic visit with worsening diarrhea, abdominal pain, rashes, facial flushing, itching, rhinosinusitis

- Rashes occurring on the trunk, arms, legs; very itchy, present for 1-12 hours, then would fade while appearing more prominent in other locations
- Rashes similar in quality to previous MCAS rashes before initiation of MCAS treatment
- Loose stool with stool urgency 6x per day, often immediately after eating
- Post-prandial abdominal discomfort to most foods and usual oral medications
- Stuffy nose and sinuses with mild frontal sinus headache and difficulty sleeping due to effect of congestion on breathing

# History of Present Illness

- No recent clear environmental allergen exposures (food allergy, new detergent, new medications, jewelry, chemical exposure, etc.)
- No recent episodes of post-exertional malaise (PEM)
- Vitals: AF; BP: 98/60 (usually 110/70), P: 92; RR: 12; SpO2: 97%
- Recent CMP, CBC, ESR, CRP all within normal limits
- Seen by dermatology, no skin biopsy performed. Given topical triamcinolone cream.
- Mild relief of itching and local rash with triamcinolone, but new areas of involvement kept emerging



# History of Present Illness

## Current MCAS therapy:

- 50 mg (2.5 mL) of Gastrocrom 15 minutes before meals and medications
- 200 mg of compounded cromolyn sodium tid
- 1 mg of ketotifen po bid
- 10 mg of montelukast
- 180 mg of fexofenadine po daily
- 20 mg of famotidine po bid
- 50 mg of diphenhydramine po prn



# History of Present Illness

- Had additionally been noting increasing dyspnea with exertion, palpitations when going up stairs, dizziness upon standing or remaining upright, exhaustion and feeling unwell when taking showers, decreased appetite, temperature intolerance
- Season was shifting to summer and weather had started becoming hot; she had a swamp cooler but no central AC in her home
- Admitted to being less stringent about her oral fluid and sodium intake than she had in the past
- Not using compression stockings as it was “too hot” and as they seemed to contribute to further lower extremity itching and redness when removed after having worn them for >1 hour

# History of Present Illness

## Current Orthostatic Intolerance/POTS Therapy:

- 80 ounces oral free water intake
- 2 packets of Liquid IV (500 mg Na) daily
- 0.1 mg of fludrocortisone po daily
- 60 mg of pyridostigmine po tid (dose limited by loose stool and mild fasciculations)
- 2.5 mg of midodrine po tid (dose limited by pruritis and paresthesias)
- 25 mg of atenolol po bid

# Clinical Interventions

- Switched from short-acting pyridostigmine to 180 mg **pyridostigmine ER**, then upward to 1.5 tabs of 180 mg of pyridostigmine ER
  - a.) ER formulation can reduce side effects including loose stool and fasciculations
  - b.) ER formulation can be cut in half and still retain ER benefits
- Midodrine discontinued in favor of **droxidopa**; started at 100 mg po tid and increased to 200 mg po tid
  - a.) Droxidopa often much better tolerated than midodrine if experiencing sensory neurological side effects with midodrine
- Increase oral fluid and sodium intake
- Gastrocrom dose increased from 2.5 mL (50 mg) to 5 mL (100 mg) per dose before meals and medications
- 10 mg of prednisone x3 days, 5 mg of prednisone x5 days, prednisone stopped

# Clinical Outcomes

- Rash outbreaks resolved
- Itching skin minimal, would require prn diphenhydramine for itching after a shower, maybe one additional time per week
- Stool formation improved, 1-2 stools per day
- Only 1-2 episodes of post-prandial discomfort per week
- Rhinosinusitis cleared up and sleep improved with improved breathing
- Less dyspnea on exertion
- Less palpitations
- Improved fatigue and exercise capacity (no longer struggling going up stairs)
- Blood pressure rose to 112/74, resting pulse reduced to 76 bpm

Physiological stress as the result of  
dysautonomia can drive other  
pathologies, like mast cell activation  
syndrome (MCAS)!

# Questions?



# THANK YOU



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