Long COVID & Post-Viral Syndromes ECHO

November 2, 2023

Dysautonomia: Back Seat Drivers

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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.

ME/CFS and Post-Exertional Malaise

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FINANCIAL DISCLOSURES

Former or present principal investigator: Emit Bio, Abbott Labs, and MT group.

None of which will be discussed today.

BACKGROUND HISTORY

29 year old female with a h/o ME/CFS since age 17.

She has had a waxing and waning course but has been at fairly steady state for past year.

She has been able to complete college and is in graduate school, with time off along the way due to health.

BACKGROUND HISTORY

Comorbidities

POTS
MCAS
Small Fiber Neuropathy
Hypermobile Spectrum Disorder
Chronic Migraines
Fibromyalgia
TMJ
GI ISSUES – dysmotility/SIBO/chronic constipation
Cognitive Issues – brain fog when fatigued
Sleep – Insomnia/restless sleep

HUA

HUA – hours of upright activity, time spent with **feet on the floor** (sitting, standing, or walking) in a 24-hour period.

NORMAL/HEALTHY people – HUA 12-16 hr/24 hour

BACKGROUND HISTORY

- Pt average HUA – 7 hours/24 hr
- Attends school 4 days a week/rests and recovers 3 days a week.
- **16 good days** a month – gets dressed, drives, attends school, and prepares simple meals. She cannot exercise or do significant upright activities after school. **HUA 10 hours/24 hr.**
- **14 bad days** a month – rests, spends most of day in recliner, studies, 1 load of laundry, has groceries delivered. Pt states she has increased fatigue and general malaise on these days. **HUA 3 hours/24 hr.**

BACKGROUND HISTORY

- Chronic push/crash cycle.
- Gradual worsening over last couple of visits (HUA of 8 hr/24 hr had decreased to HUA of 7 hr/24 hr).
- Increased absences/leaving early.
- Discussed pacing and accommodations or time off, but she only had a few weeks left and wished to get through the semester.

CURRENT MEDICATION

POTS

- Midodrine 10 mg TID
- Propranolol 5 mg TID

MCAS

- Loratadine 10 mg bid
- Famotidine 20 mg bid
- Compounded cromolyn 200 mg TID
- LDN (low dose naltrexone) 3 mg QD

CURRENT MANAGEMENT

Pain and Small Fiber Neuropathy

- Baclofen 20 mg q hs
- Pregabalin 75 mg BID
- LDN 3 mg QD

Cognitive Impairment

- Supplement (luteolin, rutin, quercetin, palm olive oil)
- LDN (low dose naltrexone) 3 mg QD

Autonomic Overdrive

- Propranolol 5 mg TID

CURRENT MANAGEMENT

Insomnia

- Trazadone 50 mg q hs
- Melatonin 5 mg q hs
- Diazepam 5 mg q hs prn
  (she rarely took this)

GI issues

- Prebiotics (diet)
- Probiotic daily
- Healthy diet low in processed foods and low in histamine
- Diamine oxidase before meals

HISTORY OF PRESENT ILLNESS

Pt mom called asking for an urgent visit.

Pt had slowly declined over 2 months since last visit.

HUA 0-2.

Living with mother due to being unable to care for herself.

HISTORY OF PRESENT ILLNESS

3 weeks after visit - Completed school

24 hours after last day- worsening of all symptoms. HUA 4 hr/24 hr period.

6 weeks after visit- improved but not back to baseline, **left for family vacation**

24 hours after arrival -worsening of all symptoms

Went to dinner with family otherwise "room-bound"

7weeks after visit traveled home (long flight/layover) – Couldn't drive home and had to go home with mother, worsened over next few days. HUA 1-2hr/24 hour, sit in recliner, walk to bathroom.

9 weeks after visit – attended graduation

24 hours later – fell in shower

PHYSICAL EXAM

- T -98.2 RR-14 Pulse – 90 sitting 136 standing with assistance BP 110/70 SpO2 99%
- Gen – Pt appears tired, speaks softly and slowly but no hoarseness noted, transferred to exam table to lie down during the history due to fatigue. She lies on table on her side with hips and knees flexed.
- She is able to answer questions with help of mom. Alert and oriented x 3.
- HEENT – dilated pupils (7 mm), PEERLA, EOMI, normal TM's, oropharynx is nl
- Neck – supple, no thyromegaly, small tender ant cervical lymph nodes bilaterally <1 cm, No carotid bruits
- CV – RRR no M,G, or R. Pulses normal throughout, delayed cap refill in digits of – 4 sec

PHYSICAL EXAM

- Lungs- CTA B, no wheezes, rales, or rhonchi
- Abd- +BS ND mild epigastric tenderness, no rebound or guarding
- EXT – No edema/cyanosis
- MSK – tenderness over proximal muscle groups
- Neuro – Strength 4/5 throughout, decreased grip strength, reflexes 2+ and symmetrical throughout, CN II-XII intact, diminished vibratory sense in toes bilaterally, decreased sensation bottom of feet per monofilament exam. Negative Hoffman's sign, no clonus.
- Skin – no rash
- Joints – no swelling, no crepitus, tenderness at the SI joints bilaterally

LABS

ACTH 40 pg/ml
Cortisol 5.2 mcg/dl
Mg 2.1 mg/dL
Comp - nl

TSH 1.76 ui/U
T3 4.0 pg/ml
T4 1.60 ng/dL

Acetylcholine receptor antibodies neg
MUSK ab neg
ESR 10 mm/hr

Aldolase 4.2 ug/L
CPK 129 U/L
Myoglobin 20 ng/ml

Tryptase - nl
Histamine - nl
PGD2 - nl
24-hour urine for methylhistamine/PGD2-nl

CRP -nl
CBC – nl
UA – tr WBC

EKG – nl sinus rhythm

Tick titers were all neg

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POST-EXERTIONAL MALAISE (PEM)

- The worsening of symptoms following physical, cognitive, orthostatic, emotional and sensory stressors.
- Can occur after far exceeding energy threshold or repeated episodes of slightly exceeding energy threshold.
- Can be delayed up to 72 hours after activity.
- Often referred to as a “crash.”
- New symptoms can occur at this time.

POST EXERTIONAL MALAISE

- Common symptoms include exhaustion, brain fog, nausea, headaches, insomnia, sore throat, muscle and joint pain, and orthostatic intolerance.
- Unique to ME/CFS
- **PEM can cause permanent worsening**

INITIAL INTERVENTIONS

POTS

- Fludrocortisone 0.1 mg QD
- Pyridostigmine 7.5 mg TID (Pt very sensitive to meds)
- 2L of IV NS 3 days per week x 3 weeks (9 gm of salt /3.5 gm of sodium)

Sympathetic Overdrive

- Diazepam 5 mg bid for 1 week then decrease to 2.5 mg BID

PEM

- Counseling patient and mom regarding pacing even the smallest of activities, reduction of sensory stimuli.
- Requested that she do nothing except basic self care.

FOLLOW UP 4 WEEKS

- **General** – HUA of 1hr /24-hour period. All days are bad days.
- Minimal improvement overall.
- She could ambulate unassisted to the bathroom and kitchen.
- She could read for 15 min at a time.

- **POTS**- symptoms of orthostatic intolerance still present with exertion or having feet on the floor more than a few min at a time.

- She continued to struggle with **insomnia**, **poor appetite**, **headaches**, **fatigue and myalgias.**

	Blood pressure	Heart Rate	Pulse Pressure	Symptoms
Supine	112/78 (120/76)	77 (66)	34 (44)	
Stand 1min	120/92 (125/84)	112 (74)	28 (41)	Dizzy, blurry vision
Stand 2 min	(130/88)	(76)	(42)	Dizzy, sob, tremulous
Stand 5 min	(130/90)	(82)	(40)	
Stand 7 min	(132/90)	(89)	(42)	
Stand 10 min	(138/100)	(94)	(36)	

ADDITIONAL INTERVENTIONS

POTS

- Increase pyridostigmine to 15 mg TID
- Pt stopped fludrocortisone due to worsened headaches

Sympathetic overdrive and Cognitive impairment

- Add Aripiprazole 0.25 mg QD

PEM

- Discussed pacing
- Break down tasks into pieces that can be paced (task analysis)
- Use heart rate to guide need to rest

FOLLOW UP 8 WEEKS

General - Pt housebound but HUA up to around 2.5 hours/24 hr, overall, she felt improved but not well. She states she has about 20% improvement.

She could sit in recliner and watch tv, get dressed, eat meal with family most days, help with dinner a couple of times a week, warm food in microwave. She was able to comprehend more easily when reading.

She continued to have symptoms of **orthostatic intolerance and shortness of breath** if she ignored her watch alarms, **headaches were less intense and less often**, still had **insomnia but was falling asleep a little bit quicker.**

ADDITIONAL INTERVENTIONS

POTS

Increase Pyridostigmine 30 mg TID

Sympathetic Overdrive

Aripiprazole increase to 0.5 mg QD

Diazepam 2.5 mg BID changed to prn from scheduled dosing

Reviewed pacing, she is using heart rate to pace her activities.

12 WEEK FOLLOW UP

PRE-PEM

HUA 7 hours a day

Attended school

Prepared own meals

Lived independently

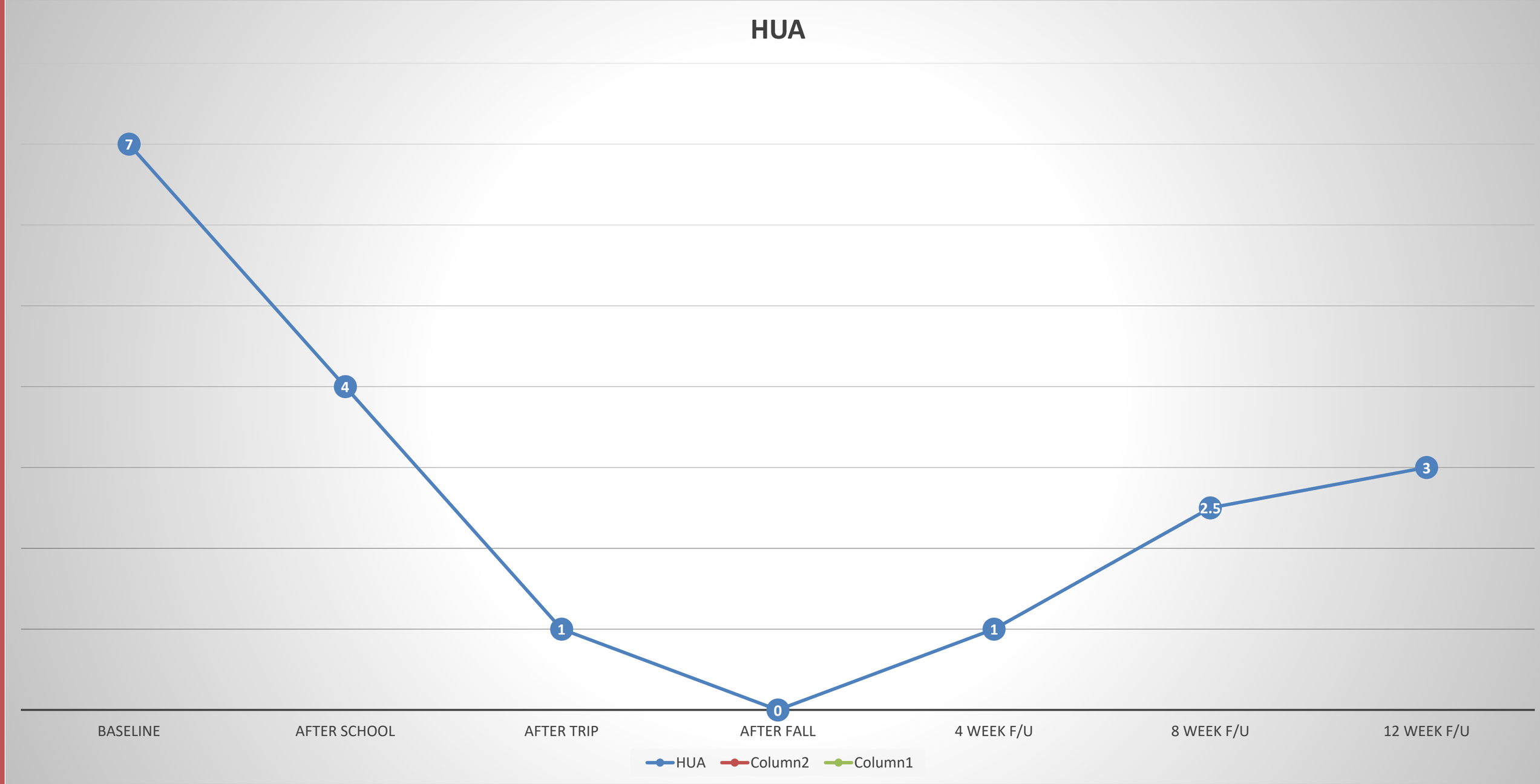
POST-PEM

HUA 3 hours a day

Lives with mother

Cannot drive or cook meal

Gets dressed every day, reads, watches TV, spends time with family, eats dinner with family, do a load of laundry, talk on the phone, feeds the pets


HUA
7
4
1
0
1
2.5
3
BASELINE
AFTER SCHOOL
AFTER TRIP
AFTER FALL
4 WEEK F/U
8 WEEK F/U
12 WEEK F/U
HUA
Column2
Column1

CONCLUSIONS

- Talk about PEM with patients early and frequently

- Pacing is key to prevention
  Frequent breaks
  Setting timers during activities
  Heart rate monitoring
  Modify activities – sit/elevate legs, handicap placard, delivery svc
  Reduce stimulation in environment

- Refer to **KNOWLEDGABLE** OT/PT

EDUCATION

- www.batemanhornecenter.org
  PEM series for health professionals
  PEM series for rehab professionals

- ME/CFS Guidebook – Bateman Horne Center

- Thursday 12/7/2023 2-3 pm EST/12-1 pm, MST
  Long Covid and Post Viral Syndrome Echo:
  When Exercise Causes Harm: OT & PT Approach to PEM
  Clayton Powers, DPT
  Amy Mooney, OTR

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Mast Cell Activation Syndrome
A backseat driver

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https://physicians.utah.edu/echo/long-covid
https://batemanhornecenter.org/providers/long-covid/project-echo/#long-covid-post-viral

No Disclosures

CASE STUDY

58-year-old woman presented to clinic 3/15/2021

CC

- Acute COVID September 2020 and concerned about Long COVID.
- Fatigue, activity intolerance, cognitive impairment, heart palpitations, tingling in her hands and feet, SOB, poor sleep, body tremors, worsening allergies and asthma.
- Newly diagnosed with Mast Cell Activation Syndrome (MCAS) by allergist a few weeks prior. Pt reported very “positive skin test.” Other MCAS labs per allergist not available.

Medications started by allergist

- Mometasone 50mcg NS
- Levocetirizine 5mg BID
- Famotidine 20mg BID
- Montelukast 10mg QD

Prior medication

Levothyroxine 75mcg QD

Dysautonomia symptoms

- Orthostatic Intolerance (OI) on sitting, standing and walking – Lightheaded, dizzy intermittent tachycardia (100-125bpm), SOB, muscle weakness, brain fog
- Low GI motility and abd bloating, early satiety
- Sensory sensitivities to light and sound
- Numbness and tingling of hands and feet
- Dry eyes
- Poor sleep – had never been a problem before

MCAS Symptoms

- **Upper respiratory:** Itchy eyes, head congestion, PND, watery eyes
- **Lower Respiratory:** SOB with any exertion
- **Gastrointestinal:** Diarrhea, GERD, increased food sensitivities
- **Dermatologic:** Generalized pruritis
- **Neurologic:** Cognitive impairment, headaches
- **Cardiac:** Tachycardia
- **Immunologic:** intermittent LAD, ST, LGF

Objective findings on PE and 10-Minute NASA Lean Test

PE:
Exam was normal
Cognition: would lose her train of thought.
MS: Hammer toes, bil.

	SBP	DBP	HR	PP/SBP
Seated	125	75	74	
Supine 2 minutes	122	78	73	36%
Standing 2 minutes	140	100	83	28%
Standing 4 minutes	130	90	80	30% - a little tired
Standing 6 minutes	140	100	84	28% - mottling of fingers
Standing 8 minutes	130	80	80	38%
Standing 10 minutes	140	90	86	35%
▲	⬆ 18	⬆ 22	⬆ 13	-Mild hypertensive response

*Prior 7-day event monitor – had 19 patient-activated transmissions with symptoms showing sinus tachycardia HR of up 122bpm.

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MCAS flares during illness

February 2022

- Busy at work and stopped her **cromolyn.** Did okay for 2 weeks then significant head congestion, sinus congestion, fever, itchy eyes, lightheaded, dizziness, fatigue and brain fog. Felt sick. COVID test negative. Resumed **cromolyn** and 3-4 days later symptoms abated. Back to baseline 10 days later.

June 2022 to September 2022

- Continued improvement in function and cognition.
- August 2022 overexerted on her treadmill, 2 days later developed diarrhea and mild h/a, runny nose, PND, sneezing, ST, LGF, increased generalized itching, worsening fatigue and OI symptoms. COVID testing negative. Rested in bed for 2 days and started to improve.

MCAS flares(cont)

March 2023

- Performing at her FT job well, better energy, almost normal cognition, tolerating some mild to moderate exercise, mostly walking, dysautonomia symptoms were pretty much resolved. Then decided to wean off **ALL** her MCAS medications.
  - Levocetirizine 5mg BID
  - Famotidine 40mg BID
  - Montelukast 10mg QD
  - Cromolyn 100mg/5cc ampules – 2 Ampules QID
- About 4 weeks into the wean she developed severe GERD, significant congestion, sneezing, itching all over her body.
- Then dysautonomia flared with increased tachycardia – even at night, anxiety, dizziness, and disequilibrium. Definitely in PEM.
- Resumed ALL her MCAS meds – MCAS symptoms resolved in two weeks, but dysautonomia symptoms persisted.

MCAS flares (cont)

May 2023

- Dysautonomia/OI symptoms still present but definitely getting better. Reintroduced 1000mg sodium with LMNT electrolytes to her water.
- MCAS symptoms well controlled.
- Able to exercise with floor yoga and 8000 steps a day at work and at home.
- By the end of the week feeling more tired and a little MCAS flaring but resolves with rest.
- Started **dextromethorphan** 15mg PRN.

Presently

- MCAS symptoms wax and wane. Overexertion is a primary trigger but has others as well. Now getting hives. Flares always worsened her OI symptoms.
- Learning to recognizing MCAS triggers such as over exertion, foods, weather, viral illnesses, poor sleep, emotional exertion.
- Learning to recognize early signs of an MCAS flare. Often looks like a cold, so can be misleading.

Present Treatment Plan

MCAS Regimen

- Levocetirizine 5mg BID
- Famotidine 40mg BID
- Montelukast 10mg QD
- Cromolyn 100mg/5cc ampules – 2 Amps QID
- Albuterol inhaler PRN
- Low histamine diet – strict

Dysautonomia Regimen

- Dextromethorphan 15mg BID
- 4L water and 1000mg Sodium

Other interventions

- Levothyroxine 88mcg QD
- CPAP

Life-style changes

- Pacing – monitoring for MCAS and PEM symptoms
- Light exercise – presently walking 20 mins a day

MCAS symptoms by system seen in Long COVID and other post infectious syndromes

If 2 or more body systems are positive for symptoms, consider MCAS

Constitutional: Fatigue, fevers, chills, weight loss

ENT: Conjunctivitis, rhinitis, sinusitis, anosmia, tinnitus, hearing loss, sore throat dysgeusia/ageusia

Neurologic: Headaches, brain fog, anxiety/depression, insomnia, seizures

Cardiovascular: Chest pain, palpitations, wheezing

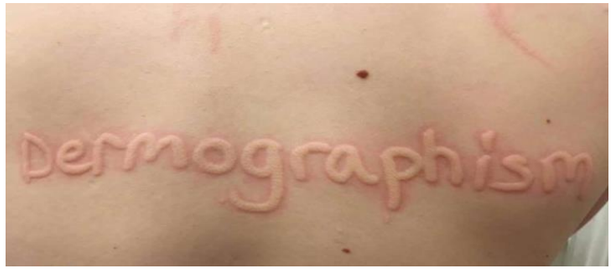
GI: Heartburn, GERD, N/v, Abd bloating, food intolerances, diarrhea/constipation

Salivary Glands: Swelling

Lymphatics: Lymphadenopathy

Dermatologic: Urticaria, flushing, pruritis, rashes, alopecia

Musculoskeletal: Myalgias, arthralgia, edema



Afrin LB, Weinstock LB, Molderings GJ. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. Int J Infect Dis. 2020 Nov;100:327-332. doi: 10.1016/j.ijid.2020.09.016. Epub 2020 Sep 10. PMID: 32920235; PMCID: PMC7529115. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7529115/

Diagnosing Mast Cell Activation Syndrome (MCAS)

Evidence of an elevation in a validated urinary or serum marker of mast cell activation:

- Total serum **tryptase** (very specific for mast cells)
- Elevated serum **histamine**

- Biopsy tissue (i.e. GI tissue) with staining positive for mast cells (CD 117 staining)
- 24-hour urine levels of:
  - **N-methylhistamine**
  - **11B -Prostaglandin F2α** (11B-PGF2α)
  - **Leukotriene E4 (LTE4)**

REMEMBER: If you have a clinical suspicion for MCAS empiric trials of therapy can also be diagnostic!

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Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. Gerhard J Molderings et al…Afrin. Journal of Hematology & Oncology 20114:10. **https://doi.org/10.1186/1756-8722-4-10©. 2011**

Mast Cell Activation/Hypersensitivity Triggers

- Heat, cold or sudden temperature changes
- Stress: emotional, physical, including pain, or environmental (i.e., weather changes, pollution, pollen, pet dander, etc.)
- Exercise
- Fatigue
- Food or beverages, including alcohol
- Drug (opioids, NSAIDS, antibiotics and some local anesthetics) and contrast dyes
- Natural odors, chemical odors, perfumes and scents
- Venoms
- Infections (viral, bacterial, fungal)
- Mechanical irritation, friction, vibration
- Sun/sunlight

MCAS Therapy options

Non-sedating Histamine 1 blockers

- Cetirizine 10mg QHS
- Loratadine 10mg QD
- Levocetirizine 5mg QD

  Can be more activating
- Fexofenadine 180mg

  Don't see this used much

Histamine 2 blockers

- Famotidine 20-40mg QD-BID

Non pharmacologic treatments

- Low inflammatory or Low histamine diets
- Diamine Oxidase – 4.2mg before meals

  Helps breaks down excess histamines

Mast Cell Stabilizers

- Cromolyn Sol 100mg/5ml 1-2 amps QID

Compounded Medications

- Ketotifen 1-2mg QD-BID

  May be a good option if not tolerating the cromolyn solution.
- Cromolyn Capsules 200mg TID

  Sometimes works more broadly than the solution. Particularly good for occipital headaches and dermatologic symptoms.

Other

- Montelukast 10mg QD
- Steroid inhalers

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Clinical Pearls

- MCAS is frequently playing a larger role in Post Viral Fatigue Syndromes than one would think. Screen for MCAS initially and frequently.

- Suspect MCAS if OI treatments not making a big difference or if the person has a lot of medication sensitivities. When initiating medications start low dose and increase slowly. Lessens reactions.

- Some MCAS and dysautonomia symptoms overlap, making it challenging to distinguish them from one another.

- MCAS screening labs are very misleading and are often negative. Rely on clinical picture and response to empiric therapy and not on laboratory data.

- H1/H2 blockers are considered the starting point for therapy. However, for more severely affected patients, I am increasingly starting with mast cell stabilizers. Why? Mast cell activation results in histamine release, among 150 other mediators, causing MCAS symptoms. So why not start with the source.

- Diet can play a big role, so counsel on low inflammatory or low histamine diets.

THANKS

Case 3 Vignette: Occult Craniocervical Instability (CCI)

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https://physicians.utah.edu/echo/long-covid
https://batemanhornecenter.org/providers/long-covid/project-echo/#long-covid-post-viral

History of Present Illness:

37 y.o. female with ME/CFS, POTS/OI by 10-minute standing passive (NASA Lean) test, gastric and small intestinal dysmotility, MCAS, chronic recurrent headaches and migraines, hEDS, and post-herpetic neuralgia presenting to a follow-up clinic visit with a **sudden and dramatic reduction in function with notable symptom increase after** catching a **viral gastroenteritis** from her husband (who worked as a teacher in an elementary school).

- Several episodes of forceful, urgent emesis with the initial infection.

- Symptoms had persisted for over a month after having recovered from the gastroenteritis without improvement.

History of Present Illness:

- Had been previously enjoying approximately 3 hours of upright activity (with feet on the ground) per day and approximately 8 hours of cognitive clarity and ability to enjoy and interact with life in a recliner chair.

- Now tolerating <10 minutes of upright activity (essentially back and forth to use the restroom) with only 1-2 hours of time tolerated in her recliner, most of which was spent sleeping or in pain with her eyes closed, disengaged from her surroundings.

History of Present Illness:

- Experiencing persistent headache and head pressure with foci of discomfort at the base of the skull and above the left eye → similar in phenotype to one of two usual headaches, but this headache was more persistent and intense than previous headaches and did not improve with acetaminophen, ibuprofen, tramadol, diphenhydramine.

- Significant dizziness, palpitations, leg weakness and tremors, and feelings of near-syncope with mild orthostatic challenge, reminding her of her symptoms prior to initiating aggressive orthostatic intolerance therapies in the past.

History of Present Illness:

- Minimal appetite with significant anorexia, early satiety, nausea, bloating with minimal food or even oral water intake.

- Mental status and overall degree of pain did not remind her of her usual prodrome of post-exertional malaise (PEM).

History of Present Illness:

- Vitals: AF; BP: 158/88 (usually 112/72), P: 94; RR: 12; SpO2: 98%
- Recent CMP, CBC, ESR, CRP, TSH all within normal limits
- Stool viral PCR negative; stool O&P negative; fecal calprotectin low

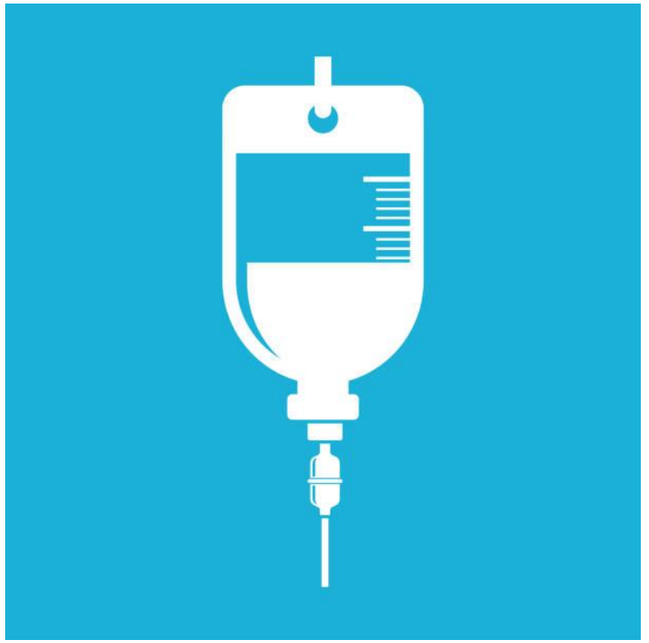
Current Pharmacotherapy:

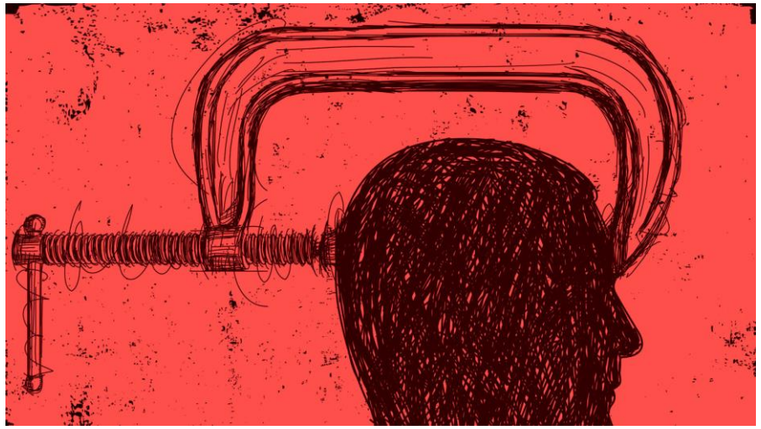
- 180 mg of pyridostigmine ER qd
- 7.5 mg of midodrine tid
- 50 mg (2.5 mL) of Gastrocrom 15 minutes before meals and medications
- 200 mg of compounded cromolyn sodium tid
- 10 mg of montelukast qd
- 10 mg of dextroamphetamine-amphetamine ER qd
- 3 mg of LDN qd
- 1 mg of aripiprazole qd
- 120 mg Emgality subq every month
- 75 mg Nurtec prn headache
- 25 mg of amitriptyline qHS
- 20 mg of fluoxetine qd

Clinical Interventions:

- Given 1.5L of IV normal saline x4 days per week for two weeks to help improve intravascular volume in the context of anorexia and nausea.

- Pulse, heart rate variability, anorexia, nausea all improved with saline, but headaches, fatigue, orthostatic intolerance and functional capacity remained essentially unchanged.





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Clinical Interventions:

- Began performing upright cervical traction using an Aspen Vista multipost for 5-15 minutes twice daily, cranking the traction up as she could tolerate (which gradually increased over time)

- Would also wear a soft cervical collar after episodes of cervical traction for upright cervical support for up to 3-4 hours per day

- Later began isometric neck physical therapy exercises to help maintain the updated anatomical positioning potentiated by cervical traction and support

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Clinical Outcomes:

- Headaches immediately mitigated with initial traction efforts, and eventually resolved with more consistent, repeated traction.
- Mental clarity and sense of debilitating fatigue improved when in active cervical traction, even if neck muscles were tight and strained.
- Blood pressure returned to previous, lower baseline and orthostatic intolerance symptoms returned to previously pharmacologically managed baseline.
- Nausea, anorexia, early satiety more consistently improved, seemingly as a function of a return to improved GI motility.

Clinical Outcomes:

- Hours of upright activity and functional capacity returned to her previous pre-viral gastroenteritis baseline, and then later significantly exceeded this baseline over the following few months so long as she remained consistent with upright traction, soft cervical collar support in vehicles, and regular neck isometric PT exercises.

Sudden and dramatic reductions in functional capacity or lack of response to previously effective pharmacological interventions can have neuroanatomical (CCI/AAI/other) underpinnings.