Re-thinking the DSM Diagnosis: Psychiatric Manifestations of Mast Cell Activation Syndrome

Corrie Marinaro, ND

NHAND November 8, 2024

Clinical interests:

PASC

The "Trifecta"

Auto-immunity

Neuroinflammation

~Shaping the inflammatory response~

New England Naturopathic Health

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Waterville, ME

No financial disclosures

WORST.
BIRTHDAY.
EVER.

DSM diagnosis = neuroinflammatory state?

Limitations of conventional standard of care in psychiatric medicine

- Subjective diagnostics and prescribing
- Insufficient availability of effective therapists
- Multiple potential side effects
- Lack of compliance due to side effects and stigma
- Only target one part of the body
- Do not factor in neuroinflammation, generally
- Lack of progress blamed on insufficiently processed past trauma
- Somatic symptoms blamed on DSM dx

MCAS Clinical Diagnosis

Estimated to affect up to 17% of general population
Established in 2007, not currently included in conventional medical curricula

Most common notable symptoms:

- Skin: urticaria, itching, eczema, psoriasis, alopecia
- ENT: dry eye, tinnitus, hearing loss, rhinitis, sinusitis
- Pulmonary: asthma, dyspnea, obstructive sleep apnea
- Cardio: blood pressure lability, presyncope, edema, palpitations, CAD
- Gastro: GERD, IBS-D/IBS-C, gastroparesis, bloating, malabsorption
- GU: Interstitial cystitis, dysmenorrhea, endometriosis, vulvodynia
- Neuro: migraine, neuropathy, dysautonomia, insomnia, seizure d/o, RLS
- MSK: myalgias, osteoporosis, osteoarthritis
- Psych: ???? all of them?

PMID 25529562, 38003876

MCAS Clinical Diagnosis, continued

MCAS should be considered with:

- Recurrent/chronic mast-cell associated symptoms in 2(+) body systems
- Evidence of elevated inflammatory markers associated with mast cell activity after a reaction
- Beneficial response to histamine blockers or mast cell stabilizers

PMID 24811013

PMID 35449490

Measurable mediators of MC activity

- Rise in serum tryptase of 20% plus 2 ng/ml above baseline after a symptomatic episode
- Rise in urinary n-methylhistamine
- Rise in urinary prostaglandin-D_2 or it's metabolite 11β-prostaglandin-$F_{2\alpha}$

Challenges with capturing and processing samples limit functional use of the above criteria

https://tmsforacure.org/tests/

Clinical dx, Mast Cell Activation Society

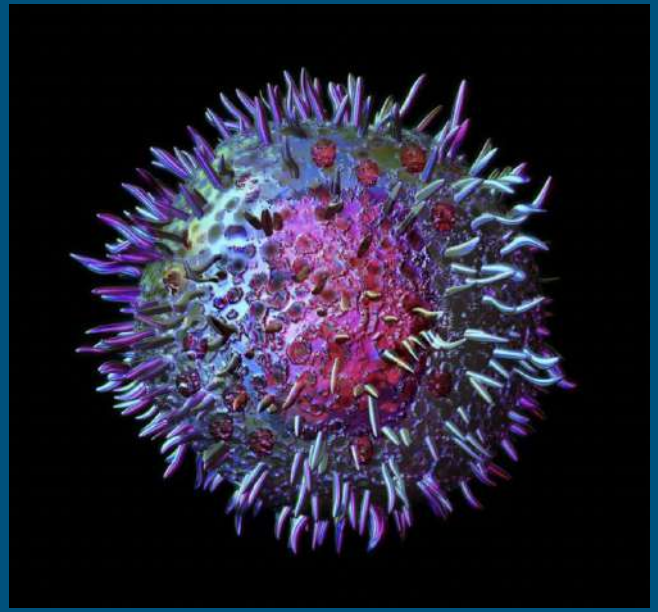
- An exhaustive workup has ruled out other medical conditions with similar symptoms and presentations
- The patient has exhibited consistent symptoms of mast cell activation in 2 or more organ systems during the same period of time, such as skin, gastrointestinal tract, central nervous system, etc.
- The patient responds to anti mediator therapy
- The patient is monitored on a regular basis, with testing for mediator rises performed periodically, by a mast cell or other specialist and/or in conjunction with an established local allergist or other physician
- The patient is evaluated for other disease processes on an ongoing basis in order to be inclusive of any new changes in the patient's condition

SNPs → MCAS predisposition

Epi-genetic triggers → MCAS pathology

MCAS can and should be a temporary condition

MC Biology



PMID 26779180
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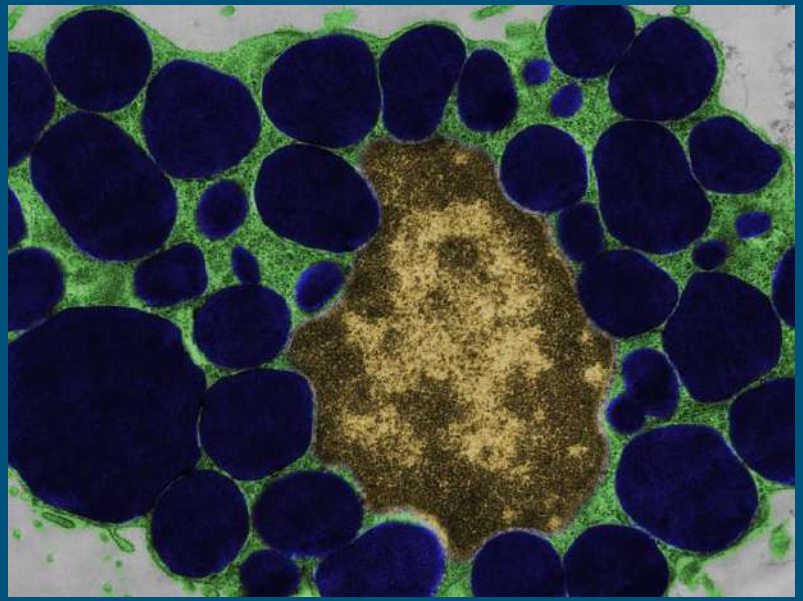
- Originate in bone marrow, mature under influence of cytokines in the microenvironment it will guard
- Skin MC are repopulated by clone cells that may be life-long
- Found in all mucosal, epithelial tissues at junction of inside and outside worlds, within connective tissues
- Patrol for antigens as immune sentinels and coordinate both innate and adaptive immune responses
- “Canonical” recognition for role in anaphylaxis and allergic phenomena
- Growing “non-Canonical” recognition for role in antimicrobial response

MC Activation, normal circumstances

- 30+ recognized receptors for various types of SPECIFIC activation states
- Other than classic IgE receptor, MC can be activated by:
  - LPS
  - Hormones including estrogens, testosterone, cortisol
  - Complement proteins C3a and C5a
  - PAMPs and DAMPs
  - Viral proteins
  - Substance P
  - Reactive T cells
- Upon activation, MC release mediators of vascular permeability, adhesion and extravasation for purposes of recruitment
- MC also initiate an immune response with ROS, MC-specific proteases and exosomes to engulf pathogens

PMID 380664133, 26779180, 38638437

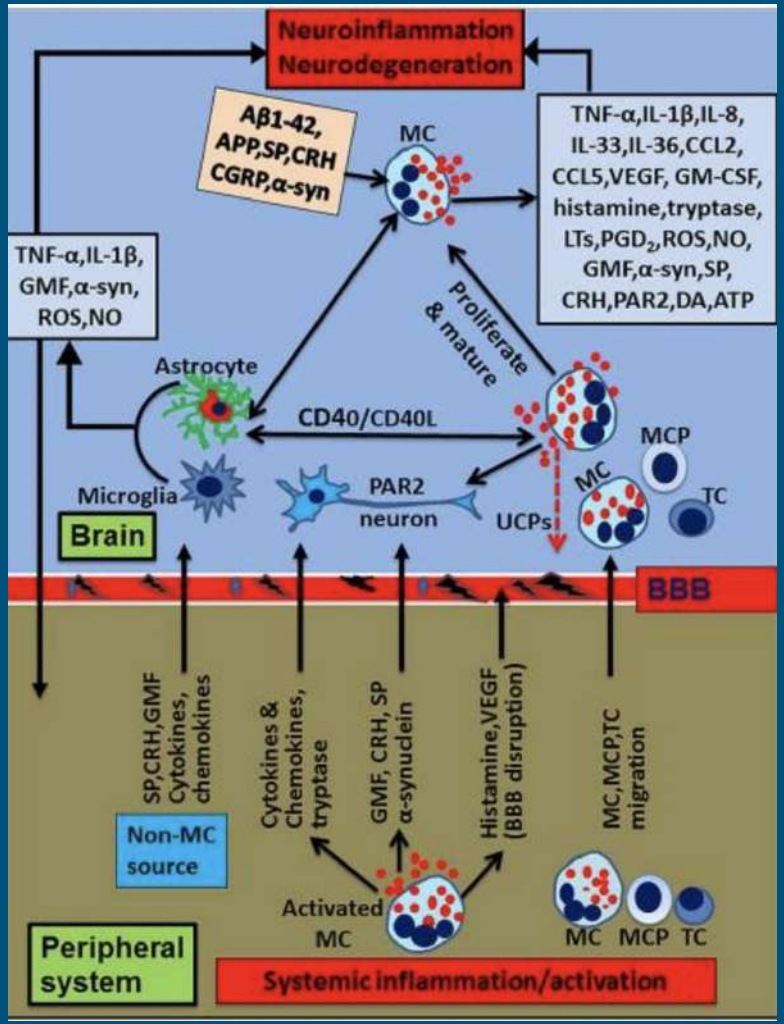
MC Implication in Neuroinflammation



MC are found on the brain side of the BBB
Degranulation of MC in response to immune stimuli →

- Histamine/serotonin/dopamine: vasoactive neurotransmitters
- Cortisol: anti-inflammatory
- Cytokines IL-1-6, PAF, LT's, PG's: recruit and hold the door for leukocytes
- NO/VIP/VEGF: increase blood flow to threatened area
- TNF alpha/ROS: apoptosis/necrosis
- Collagenases/MC-specific proteases: tissue degradation
- Renin/Angiotensin II: regulate BP for immune response

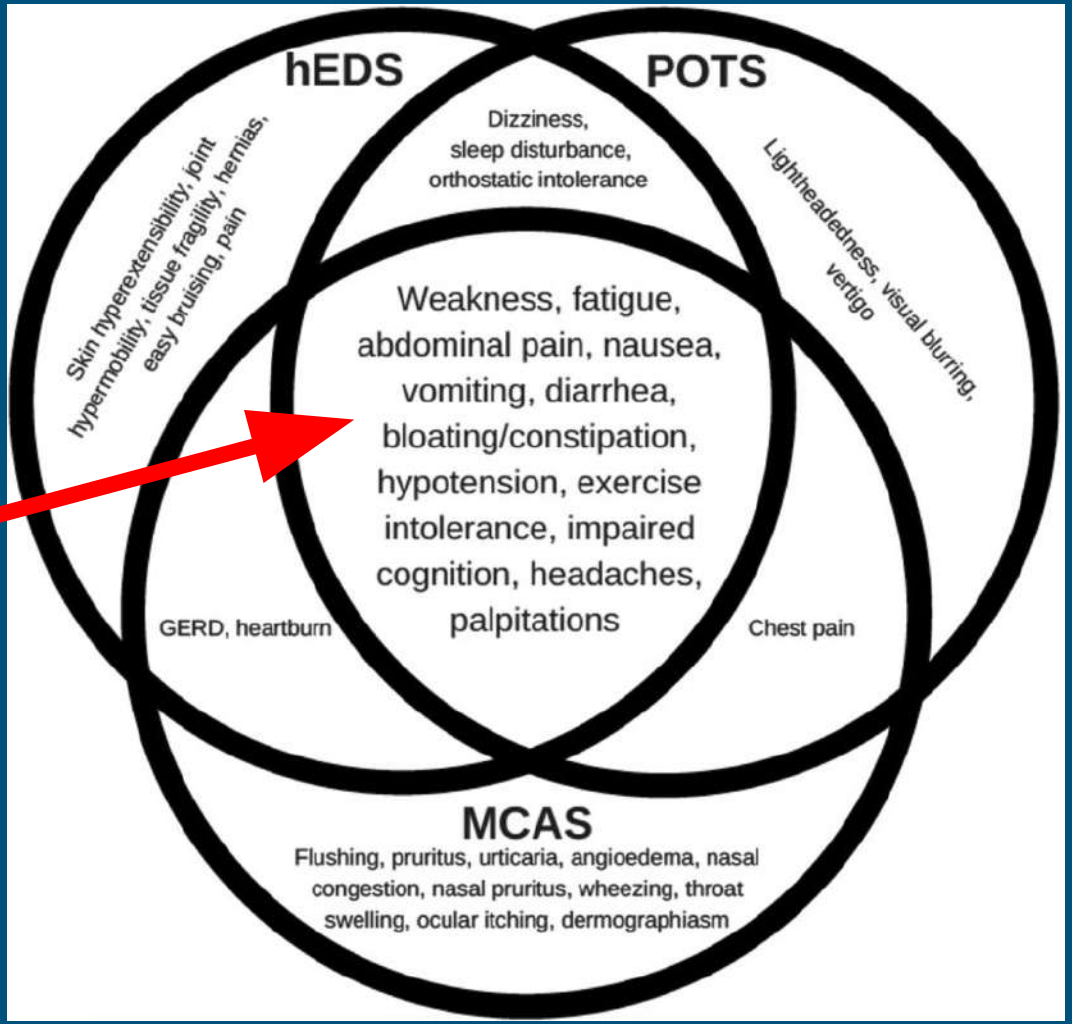
PMID 25529562, 22125569, 28790893



- MC present in meninges and can migrate into brain under normal conditions
- CNS MC population increases during perceived threat
- MC have reciprocal relationships with Microglia, Astrocytes, Oligodendrocytes
- Microglia express all 4 histamine receptors, Astrocytes express H1, H4
- Microglia and MC engage in pro-inflammatory crosstalk
- MC proteases → PAR 2 → neuronal cell death
- MC- induced inflammatory neuronal signaling downregulates expression of uncoupling proteins → neurodegeneration

PMID 28790893, 25529562

Some sort of DSM Diagnosis



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Journal of Personalized Medicine

MDPI

Article

Neuropsychiatric Manifestations of Mast Cell Activation Syndrome and Response to Mast-Cell-Directed Treatment: A Case Series

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Abstract: Mast cell activation syndrome (MCAS) is an immune disease with an estimated prevalence of 17%. Mast cell chemical mediators lead to heterogeneous multisystemic inflammatory and allergic manifestations. This syndrome is associated with various neurologic and psychiatric disorders, including headache, dysautonomia, depression, generalized anxiety disorder, and many others. Although MCAS is common, it is rarely recognized, and thus, patients can suffer for decades. The syndrome is caused by aberrant mast cell reactivity due to the mutation of the controller gene. A case series is presented herein including eight patients with significant neuropsychiatric disorders that were often refractory to standard medical therapeutics. Five patients had depression, five had generalized anxiety disorder, and four had panic disorder. Other psychiatric disorders included attention-deficit hyperactivity disorder, obsessive compulsive disorder, phobias, and bipolar disorder. All eight patients were subsequently diagnosed with mast cell activation syndrome; six had comorbid autonomic disorders, the most common being postural orthostatic tachycardia syndrome; and four had hypermobile Ehlers-Danlos syndrome. All patients experienced significant improvements regarding neuropsychiatric and multisystemic symptoms after mast-cell-directed therapy. In neuropsychiatric patients who have systemic symptoms and syndromes, it is important to consider the presence of an underlying or comorbid MCAS.

Keywords: anxiety; depression; dysautonomia; mast cell activation syndrome; panic disorder; POTS

check for updates

Citation: Weinstock, L.B.; Nelson, R.M.; Blitshteyn, S. Neuropsychiatric Manifestations of Mast Cell Activation Syndrome and Response to Mast-Cell-Directed Treatment: A Case Series. *J. Pers. Med.* **2023**, *13*, 1562. https://doi.org/10.3390/jpm13111562

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1. Introduction

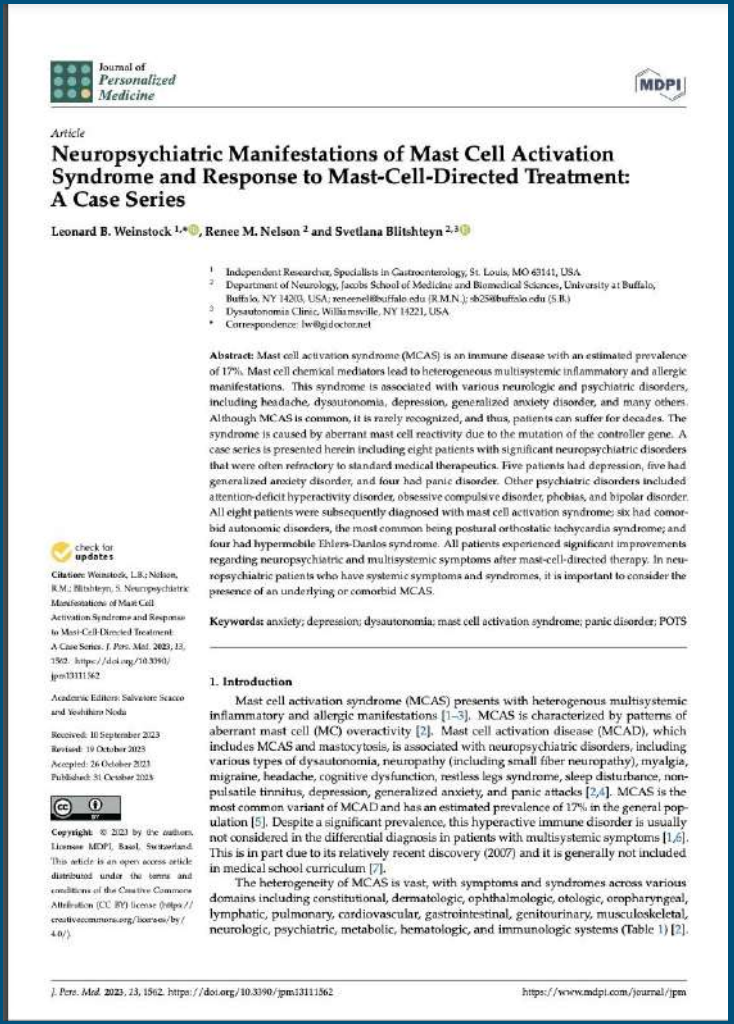
Mast cell activation syndrome (MCAS) presents with heterogenous multisystemic inflammatory and allergic manifestations [1–3]. MCAS is characterized by patterns of aberrant mast cell (MC) overactivity [2]. Mast cell activation disease (MCAD), which includes MCAS and mastocytosis, is associated with neuropsychiatric disorders, including various types of dysautonomia, neuropathy (including small fiber neuropathy), myalgia, migraine, headache, cognitive dysfunction, restless legs syndrome, sleep disturbance, non-pulsatile tinnitus, depression, generalized anxiety, and panic attacks [2,4]. MCAS is the most common variant of MCAD and has an estimated prevalence of 17% in the general population [5]. Despite a significant prevalence, this hyperactive immune disorder is usually not considered in the differential diagnosis in patients with multisystemic symptoms [1,6]. This is in part due to its relatively recent discovery (2007) and it is generally not included in medical school curriculum [7].

The heterogeneity of MCAS is vast, with symptoms and syndromes across various domains including constitutional, dermatologic, ophthalmologic, otologic, oropharyngeal, lymphatic, pulmonary, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, neurologic, psychiatric, metabolic, hematologic, and immunologic systems (Table 1) [2].

Case series of 8 patients with debilitating neuropsychiatric d/o refractory to conventional therapies (5 x MDD, 5 x GAD, 4 x PAD; other comorbidities ADHD, OCD, phobias, BPD, Tourette's, Narcolepsy)
All 8 dx'd with MCAS through lab markers
6 x POTS, 4 x EDS

- 1st line: 3-week trial on gf, df, low-histamine diet +
- Non-sedating H1-blocker and H2 blocker BID
- 2nd line added Vit C, Vit D, Quercetin
- 3rd line added LDN
- 4th line added chemotherapeutic agent hydroxyurea

PMID 38003876



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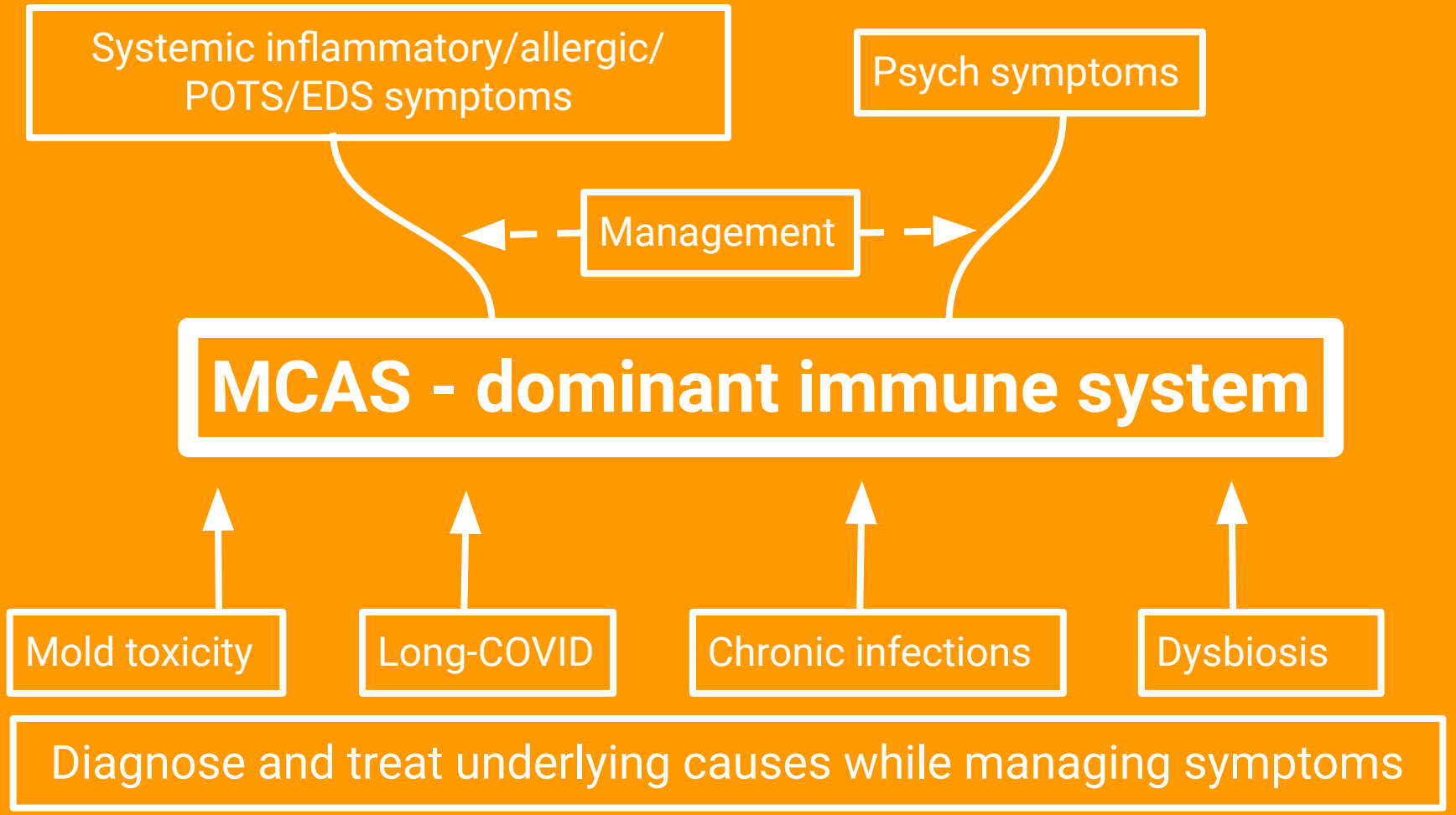
- 6 patients experienced full resolution of MC and Psych sx and returned to work full time
- 1 patient returned to full function as homemaker with daily suicidal ideation x decades resolved
- 1 patient improved enough to return to work part-time, this was only partial response in the case study

"The mislabeling of these patients with psychiatric illness as the cause for a systemic illness often leads to inappropriate or misdirected treatment, iatrogenic adverse events, resentment, mistrust on the part of the patient, doctor shopping, non-compliance, medical care avoidance and psychological symptoms and trauma caused by their negative experience with the healthcare system"

BUT WHAT'S CAUSING THE MCAS-MEDIATED NEUROINFLAMMATION??


Systemic inflammatory/allergic/
POTS/EDS symptoms
Psych symptoms
Management
MCAS - dominant immune system
Mold toxicity
Long-COVID
Chronic infections
Dysbiosis
Diagnose and treat underlying causes while managing symptoms

Case #1: PANS post Gastroenteritis

9 year old female with nausea, vomiting, diarrhea and chest pain; complaints dismissed as psychogenic; health fears
Hx of GAD, mom is therapist
Current meds: Cyproheptadine 4 mg BID
Goals: dx GI Complaints, manage psych sx w/o medication

FOC May 2022

- We meet by zoom as patient does not feel well enough to leave the house
- Complaints of nausea, chest pain, sore throat, bloating after meals, bad taste in mouth
- Onset in February after family vacation to PR where she has been many times
- Patient is convinced she is dying, desires constant reassurance that she isn't, cannot sleep by herself
- Has missed 30+ days of school in the past three months
- Currently using Cyproheptadine 4 mg BID rx'd by Pediatric GI Specialist, causing sedation and ravenous eating
- Has been tested for H Pylori based on father's recent dx with similar symptoms but no other workup
- Pediatrician has attributed GI symptoms to anxiety and recommended SSRIs

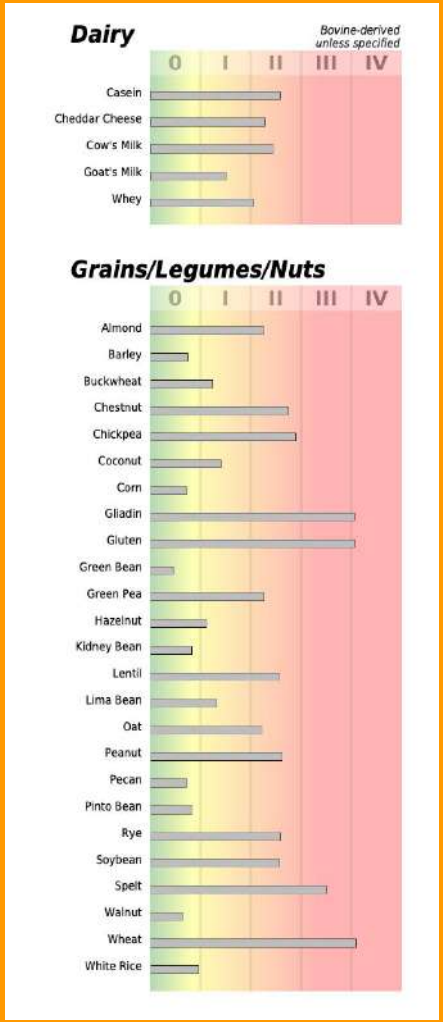
Pertinent History

- Hx of tonsillar and adenoid hypertrophy with tonsillar scraping at age 8
- Episodes of anxiety starting at age 5 and has frequently refused to go to school due to health fears around COVID
- Parents eat a plant-based diet, patients is primarily plant based as well; low-FODMAP nutrition plan is challenging
- Currently cyproheptadine helping with GI symptoms but not anxiety and health fears and causing multiple side effects

First steps and results

- PCR stool analysis:
  - Dientamoeba Fragilis
  - multiple inflammatory bacterial overgrowths (not strep)
  - very low beneficial coverage and SIgA
- Plan: (half-heartedly implemented)
  - Metronidazole 250 mg BID x 30 days with spore-based probiotic
  - Plant-based digestive enzymes cc
  - Herbal antimicrobial glycerite to cover multiple food-borne illnesses
  - Cooked veg, stews, smoothies, congee; easy-to-digest foods
  - Take off AM dose of cyproheptadine as patient had entered recommended time frame for weaning
- Results:
  - parents pull cyproheptadine entirely
  - OCD/health fears and insomnia increase → patient visits ER while waiting for stool testing → dx'd with panic attack d/o and offered SSRIs again
  - parents pull all supplements and proceed with metronidazole only

What do food sensitivities really mean?



ROC July, 2022

- Patient and mother report immense improvement from metronidazole in energy, anxiety and digestion
- Had also been seen by a local doc in PR who dx'd double ear infection and rx'd amoxicillin, improvement had started prior to this
- Has also started Paxil out of desperation
- Next steps:
  - Finish metronidazole, reintroduce natural antimicrobials
  - Famotidine 20 mg AC
  - Digestive enzymes and SIBO-specific nutrition
  - Histamine-specific probiotic
  - L-theanine 200 mg up to TID
  - Add silybum glycerite 1 dropperful BID cc based on VM analysis
  - Teach parents VM techniques

L-theanine as mast cell stabilizer for brain ~and~ Parasites and the histaminergic immune system

ROC September, 2022

- Psych symptoms continue to improve and is back to “online” school, Paxil has been pulled without incident
- Follow up stool analysis:
  - Diaentomoeba fragilis clear
  - NO beneficial bacteria
  - SIgA has improved slightly
  - Eosinophil activation protein drastically elevated in spite of parasite “clear”
- Next steps:
  - Cromolyn Sodium compound 100 mg BID
  - Maintain famotidine, natural anti-microbials, probiotics
  - EMDR or similar
  - Work up mycotoxin urinalysis based on mom’s suspicions about the family house
  - Check tick borne illness panel

Cromolyn Sodium as Mast Cell Stabilizer

ROC November 2022

- Update:
  - GI sx are resolved, patient would like to reintroduce gluten
  - Parents are in the midst of remediation after basement flooding
  - Back to swim, dancing, being active
  - Focus is improved with school work
  - Ongoing occasional episodes of chest pain without pattern, can now talk herself through them with coping mechanisms
  - Ongoing high somatic awareness
  - Ongoing allergic rhinitis
- Mycotoxin levels and tick-borne illness panel are essentially negative
- Plan:
  - maintain Cromolyn, natural antimicrobials, L-theanine prn and cholagogues (choline + silybum)

ROC January- March, 2023

- Backtracking:
  - Patient develops UTI/Kidney infection, culture demo Beta strep
  - Non-stop intrusive thoughts and panic attacks; this does not change with clearing UTI
  - Consuming ice cream nightly in large amounts and allergic rhinitis is increased
  - Has been out of “online” school for 4 weeks and not participating in swim, dance
  - Parents are in midst of mold remediation and notice exacerbation when she is in the house
- Parents initiate guanfacine and sertraline under advice of psych prescriber/therapist
- Patient becomes focused on genitalia and new rumination turns to whether she is a boy or a girl
- We d/c Cromolyn Sodium based on no residual gut sx
- We rx LDN, herbal PANS protocols (parents do not initiate)
- We rx Nystatin 500,000 IU once daily x 8 weeks and fluconazole 200 mg once weekly x 8 weeks based on revelations of chronic athlete’s foot and fungal rashes

March - September, 2023

- Patient improves drastically with antifungals
- Asymptomatic from April - September 2023 when she contracted COVID; she is now recovering with continued sinus congestion and slight (manageable) flare in obsessive thoughts
- She has started menses
- She has reintroduced all foods, does continue to have GI pain/distress after gluten and sugar and mucus production after dairy
- Family would like to wean SSRI and guanfacine

We clean up residual sinusitis, restart natural antimicrobials and diversify herbal mast cell stabilizers with ongoing L-theanine

Role of menarche in PANS...not all bad news

October 2023 - August 2024

- Patient is able to d/c guanfacine first then slow wean of sertraline without backtracking
- Mental health is stable and initiated transition back to school on her own; participating in multiple athletic activities
- Ongoing allergic complaints and frequent illness
- Currently recovering from COVID and in the aftermath some panic attack symptoms have returned, these are manageable with coping mechanisms
- House has been completely remediated
- Gut is stable
- Growing substantially

Next steps in this case

- Immune system, Immune system, Immune system
- Re-work mycotoxin urinalysis now that house is supposedly safe
- Sustained focus on building IgA secretion
- How to handle food….?

Case #2 rural medicine at its worst and patient motivation at its best

32 year old female with dx MDD, GAD, PMDD, PTSD
Rx: venlafaxine ER 225 mg q AM, bupropion ER 450 mg q AM, hydroxyzine 100 mg q AM, glucophage 500 mg BID, OCP
Goals: “I don’t want to feel crappy and unhealthy anymore”

FOC: April 2023

Complaints of:

- Frequent incessant panic attacks since COVID (GI sx only and never + test)
- ~4 hours restless sleep nightly, easily falling asleep at work/while driving
- GERD and loose stools, requires antacids all day every day
- With OCP: irregular heavy menses but not incapacitating
- High levels of stress in current job and relationship, living in a small apartment above her boyfriend's auto repair shop
- No follow up with PCP or psych prescriber since prior to pandemic, VERY unmotivated to return

Pertinent History

- Very traumatic childhood and started “journey” of psych meds after sexual assault at 17
- “When not on medication I spiral into a very dark place and relive my childhood trauma and sexual assault”
- Has always had IBS, worse post COVID
- Chronic vaginitis repeatedly treated with miconazole and metronidazole creams, does not like to acknowledge this area of her body
- Was dx’d with PCOS after developed acne and facial hair during a change of OCPs

PE/impressions

- Neuro: patient is barely awake, struggles with word-finding, desperately wants to convey thoughts
- ENT: diffuse bilateral lymphatic congestion, evidence of PND, hypertrophic tonsils
- Cardio: tachycardia, “thready” pulse
- Abdominal: water retention, tenderness to palpation universal
- Pelvic: bilateral ovarian cysts L > R
- No gyn exam in this visit

FOC, first moves

- Refer to colleague FNP psych prescriber
- Move hydroxyzine to evening
- Pull glucophage
- Add famotidine 20 mg BID prior to meals, cetirizine 10 mg BID
- Initiate L-tyrosine 1,000 mg AM and afternoon, 5-HTP 100 mg BID
- Order annual blood work

Barriers to successful psychiatric care

Pertinent lab findings

- Trigs 317, nl TC, LDL, HDL
- WBC 12.6, neutrophilia, lymphocytopenia
- Platelets 476
- hs-CRP 10.3
- Vit D 28
- TSH 2.66

ROC May 2023

- Update: had d/c'd hydroxyzine on her own, happier, more energy, sleeping better, GERD and loose stools improved
- Has not contacted psych-NP referral
- Switched birth control to hormonal IUD , fear of old sx returning: add progesterone USP 100 mg qhs for first 3 months of transition
- Add liquid Vit D 6,000 IU qd until re-check
- Add NP Thyroid 60 mg on waking
- Order tick borne illness studies
- Nutrition counseling on glycemic stability

ROC June 2023

- Tick borne illness studies are essentially negative?
- Energy + mood, IBS, sleep are all improved
- Panic attacks are resolved
- Has lost 20 lbs with improved appetite
- Plan: reduce infectious burden with broad spectrum herbal antimicrobial support to cover gut and systemic infections (does contain echinachea) and probiotic geared at histamine reduction
- Patient wants to start weaning psych meds, again refer to colleague, again patient does not go

ROC August 2023: ruh roh

- Periods and PMS are back with vengeance
- Loose, urgent bowel movements after every meal
- Bupropion d/c'd the day after last visit, Venlafaxine tapered quickly over 2 week period, unsupervised and undisclosed
- "It's been a wild ride"....patient insists that s/e of meds are worse than withdrawal symptoms
- Plan:
  - Pulled anti-microbial supports and probiotics
  - Add gentle iron
  - Add gentle liver detox/lymphatic drainage support
  - Order updated labs

YIKES…
Patient autonomy in psychiatric medicine

ROC September 2023

- Periods and gut sx are calming down
- Diarrhea now centered around menses and junk food only
- Complaining of brain fog -> feelings of anxiety

Plan:

  - Reintroduce probiotics, followed by same antimicrobial supports
  - Add L-theanine for prn dosing during day and 200 mg qhs

ROC November 2023

- Update:
  - Diarrhea returned with loose stools 5-6 times per day even after pulling antimicrobials again between appointments
  - Migraines are gone
  - Revelations of current abusive relationship
- Plan:
  - Referral to talk therapy, patient does not go
  - Switch to spore-based probiotic
  - Add binders before reintroducing antimicrobials
- Result:
  - Fast forward two weeks to same result, patient advised to pull antimicrobials again and collect PCR stool analysis

ROC January 2024

- Update: all symptoms are stable other than gut, mixed IBS symptoms ongoing
- Stool analysis:
  - Salmonella
  - H Pylori
  - Proteus Mirabilis
  - Entamoeba Coli
  - numerous beneficial and opportunistic overgrowths
  - occult blood negative
  - Secretroy IgA low
  - eosinophil activation protein elevated, calprotectin nl
- Plan:
  - Restart SAME natural antimicrobial
  - S Boulardii
  - Metronidazole 250 mg qod x 28 days with spore-based probiotic
  - She improves until food poisoning in March and goes to ER for dehydration

ROC April 2024

- CT scan in ER reveals suspected colitis, triggers revelation of same in 2020 when was hospitalized for similar symptoms
- Had been referred by ER to gastroenterology who offered mesalamine but no further studies, feels that colitis will “run its course”
- Sleep is disturbed at 2-3 AM when wakes startled and difficulty going back to sleep
- I finally switch to immune-modulatory (vrs. Immune stimulating) antimicrobial approach with artemisinin and ultra LDN

Why did I not spot the pattern?? Patient communication dynamics

ROC May 2024

- Did not have spring allergies and migraines this year, no longer needs H1 blocker
- Sleep improving with ultra-LDN, trauma dreams are no longer occurring
- Gut is stable enough that we are willing to delve back into gut treatment
  - Famotidine: 20 mg before dinner
  - Biofilm disruptor: 1 cap once daily ONLY while using antimicrobials
  - Metronidazole: 250 mg every other day x 6 weeks
  - Fluconazole: 150 mg once weekly to keep yeast at bay x 6 weeks
  - Spore based probiotic: 1 cap at night, start this now to independently test it
  - Gentle liver detox/lymphagogue: take every other day on days not taking the metronidazole

ROC June 2024

- Bowel movements are stable, some bloating ongoing; constipation prior to menses and diarrhea at the start of menses
- Vaginitis is clear after 10 years of symptoms
- Has switched jobs and positioning self to leave partner
- Updated labs ordered at this visit show:
  - Hormone balance (per salivary collection) ideal, no signs of PCOS
  - Cortisol low on waking, elevated mid-day, nl rest of day
  - Hs-CRP in normal range, no anemia, WBC into normal range, continued mild neutrophilia and lymphocytopenia

Future directions

- Restore balance to gut immune system with ongoing immune-modulatory approach and reparative supports to mucosal lining
- Proteolytic enzymes to break up suspected/palpable endometriotic adhesions, discuss IUD removal
- Maintenance neurochemistry support with exploration of benefit from methylation tools
- Continue to encourage patient out of toxic living environment and into a more supportive community

Case 3: psychosis, MCAS + ALL the interventions

32 year old female recently discharged from inpatient psych care w/dx OCD, Bi-Polar 2, GAD
Rx: Lithium 450 mg BID, Olanzapine 10 mg BID, Hydroxyzine 50 mg TID, Lorazepam .5 mg TID
Goals: tolerate side effects of medication regimen

FOC May 2022

- Patient presents with mother who is her support system and advocate
- Has been recently discharged from 30 day inpatient stay after break up that triggered psychotic episodes and medications adjustments gone awry
- Current medication regimen “working”, no longer having psychotic episodes
- Is increasingly suicidal
- Side effects: perpetual feeling of throat closing and not being able to breathe
- Goals: tolerate the medication regimen, eventually not need psych meds

What is the measure of success for an acute psych regimen?

ROS

- Constitutional: Chronic fatigue, hypersomnia as S/E of psych regimen
- EENT: Right sided eye floaters, difficulty swallowing, sinus congestion, PND
- CARDIO: frequent palpitations attributed to anxiety
- GI: IBS-D, GERD
- Reproductive: ovarian cysts, PMDD, suspicion of endometriosis, IC with constant urge to urinate, chronic vaginitis
- Integumentary: eczema, psoriasis
- MSK: chronic right sided musculoskeletal complaints, neck pain, HA

MCAS city!
What are current causes?

Pertinent History

- Dx'd with OCD in high school and initiated treatment with SSRI's: ALWAYS S/E
- IBS-D symptoms developed post PID dx treated with multiple rounds of abx → appendectomy
- Prior to manic episods, flooding had occurred in her ancient NYC apt, water damage never repaired due to COVID
- Recent trauma of inpatient stay and resulting PTSD dreams

PE

- Observed tardive dyskinesia: slow speech, slow movements, word-finding challenged, memory challenged
- EENT: tonsillar hypertrophy, PND, pharyngeal erythema, lymphatic congestion
- CARDIO: bradycardic regular rate, full body edema
- GI: hiatal hernia, universal tenderness to palpation

First steps

- Ketotifen: H1 blocker/mast cell stabilizer; titrate .25 mg BID → 1 mg BID over 3 weeks
- Famotidine: 20 mg BID AC
- Review blood work ordered by previous ND:
  - Borderline hypothyroidism (prior to addition of Lithium): add SR T4 50 mcg/T3 5 mcg compound
  - Estrogen dominance with negligible progesterone: add 200 mg compounded bioidentical progesterone nightly
  - Vitamin D 25, add 5,000 IU daily liquid

Diversification of psych management

Ketotifen pros and cons

Bio Progesterone pros and cons

ROC August 2023

- Energy improved with thyroid compound
- Fewer breakthrough psych sx with progest
- Fewer histamine symptoms with ketotifen, does not feel like throat closing
- Periods are shorter and less debilitating
- Lithium had been increased to 600 mg BID due to ongoing suicidality (prior to adding ketotifen) → increased anaphylactic reactions → lithium decreased to baseline 450 mg BID → lamotrigine added at 100 mg BID with goal of weaning lithium
- Observed tardive dyskinesia worse
- Firing current psych provider, searching for a more integrative practitioner

November 2022 - Feb 2023

- Elected to undergo ECT to compensate for weaning lithium
- Fewer histamine symptoms with lithium off
- Debilitating fatigue → reduce ketotifen to nighttime dose only
- Had requested tick-borne illness workup which revealed “equivocal” Bartonella, 4 bands positive in Western Blot (visual interpretation)
- Would like to be aggressively treated for “Lyme”
- Negotiated conservative abx protocol diversified with immune-modulation herbs, anti-inflammatory biofilm disruption and spore-based probiotics
- IBS-D worsens, vaginitis worsens → abx dc’d after 6 weeks

Where is tick-borne illness in the “layers” of this case?

March 2023 - May 2023

- Psych provider has agreed to wean olanzapine by 2.5 mg increments q month due to hypersomnia and daytime fatigue
- Each decrease → temporary increase in anxiety attacks (manageable with diphenhydramine!) → increased self-awareness
- Patient has pulled ketotifen and thyroid support on her own due to suspicions they are contributing to fatigue
- Menses are occurring q 2 weeks with heavy bleeds, water retention, weight gain → progesterone decrease necessary
- Patient becoming more reactive to foods, simple nutrients, herbs, etc…
- Patient reluctantly agrees to an ERMI of her apartment, provoked mycotoxin urinalysis and sinus culture

June 2023 - revelations

Mycotoxin panel:

- Aflatoxin ~29 x safe range
- Ochratoxin ~ 8 x safe range
- MPA ~ 3 x safe range
- Citrinin ~ 2 x safe range

ERMI 26.6 Q4

Sinus culture with MARCONS and Rhodotorula

- Sick mom on the landlord to complete remediation while patient moves out, repeat ERMI 3 weeks post completion and before patient reoccupies
- Continue gentle liver detox, add binders; plan to update mycotoxin test after repeat ERMI
- Add conservative anti-fungal treatment with nystatin and herbs
- Anti-fungal compounded sinus rinse with plan to reculture at the end of 30 days

A word on mold and psychiatric symptoms ~and~ Why mycotoxin illness is an unpopular diagnosis

August 2023 - June 2024

- Apartment is remediated after mom threatens legal action
- Die-off reactions from anti-fungal regimen, patient completes first round of treatment slowly but refuses to complete any of the follow up testing
- Binders are not tolerable due to interference with medication absorption
- Continued hypersomnia, brain fog, fatigue
- Olanzapine wean continues with temporarily increased anxiety at each decrease but improved cognition and self-understanding
- With last 2.5 mg of olanzapine coming off, PTSD dreams of inpatient stay return and anxiety attacks increase; patient is advised by prescriber to increase Ativan and symptom picture worsens → patient pulls lorazepam entirely, leaving only lamotrigine 100 mg BID

July 2024

- Mom is late to zoom appointment, patient is unconcerned and eloquently recounts all of the events of the past few weeks
- Has courageously taken on benzodiazepine withdrawal after two years of BID-TID lorazepam
- She is having increased histamine reactions to foods and supplements
- She has initiated work with homeopathic Lyme protocol with another practitioner and is working through trauma with with two separate therapists utilizing different techinques
- She is journaling, making sense of the past several years, hopeful for future

Ahhhhhh….
The luxury of taking a backseat to patient’s desired directions of treatment

Future directions

- Ultra LDN and methylation support
- Bring in monitoring of body systems as well as psych symptoms to reclaim autonomy over health:
  - Gut
  - Menses
  - Allergies
- Restart mold toxicity conversation as needed, manage histamine symptoms as needed

Case #4: Inconvenient Truths, OCD/PMDD post COVID

35 year old female intolerant of psych meds
Dx of OCD, PMDD, GAD
Rx: Cefuroxime 500 mg BID, Azithromycin 250 mg BID for tx of recent Lyme and Anaplasma dx

FOC early June, 2023

- Patient presents for treatment of “Anaplasma and Lyme” dx’d on specialty testing
- She has been treating with an integrative psychiatrist, rx’s of azithromycin 250 mg BID and cefuroxime 500 mg BID x 1 month, recently finished abx w/o improvement; started LDN 3 mg on completion of regimen, felt worse and pulled
- C/o intrusive thoughts and OCD/ritualized behaviors worse in PMS week
- Sx started post COVID infection in April of 2022 and worsened when was re-infected in August of 2022
- Has been rx’d Escitalopram and other SSRIs which caused debilitating neurological side effects
- PCP initiated minocycline 25 mg for OCD sx and started to improve, developed acne which was treated as an allergic reaction and minocycline was d/c’d, improvement stopped

ROS

- Constitutional: chills, weight gain, weakness, fatigue
- ENT: sinus pressure, vision decline, intermittent HA
- Cardio: chest pain and palpitations attributed to…you guessed it…ANXIETY
- GI: constipation as baseline, severe diarrhea with antibiotics
- Neuro: sporadic dizziness, slow thinking
- Psych: anxiety, depression, OCD
- GU: excessive discharge x many years which has been told is “normal”, color is opaque, yellow/white, smells of yeast; denies itching/burning/pain with intercourse

Pertinent history

- Uncharacteristic anxiety started in 2020 when moving family of four children into a new house
- Former house had multiple animal infestations
- First COVID infection April 2022 with short acute phase, then after recovering developed dyspnea, chest pain, headache, ear pain, pressure, debilitating vertigo, numbness left side of face, nausea, vision changes with normal vision exam, diarrhea
- *****Electrolytes were helpful for the above******
- Blood work and CT scan clear, no treatment offered until began complaining of fear of being poisoned and spending weeks in bed crying; then was offered (and failed) SSRIs
- Second COVID infection in August of 2023 initiated PMS symptoms

PASC and Long-COVID POTS

PE: notable findings

- Visible hypertrophy of frontal sinuses L > R, left eye does not open to same degree as right; laterality not corroborated in neuro exam
- Diffuse lymphatic congestion
- Water retention over abdomen, retained stool palpable, multiple dense areas of scar tissue w/o hx of abdominal surgery
- Patient is fearful of discussing symptoms making goal setting difficult

Whats up with the forehead thing? Mast cell reciprocity with fibroblast → sinusitis, endometriosis often concurrent

PMID 37234076
PMID 35449490

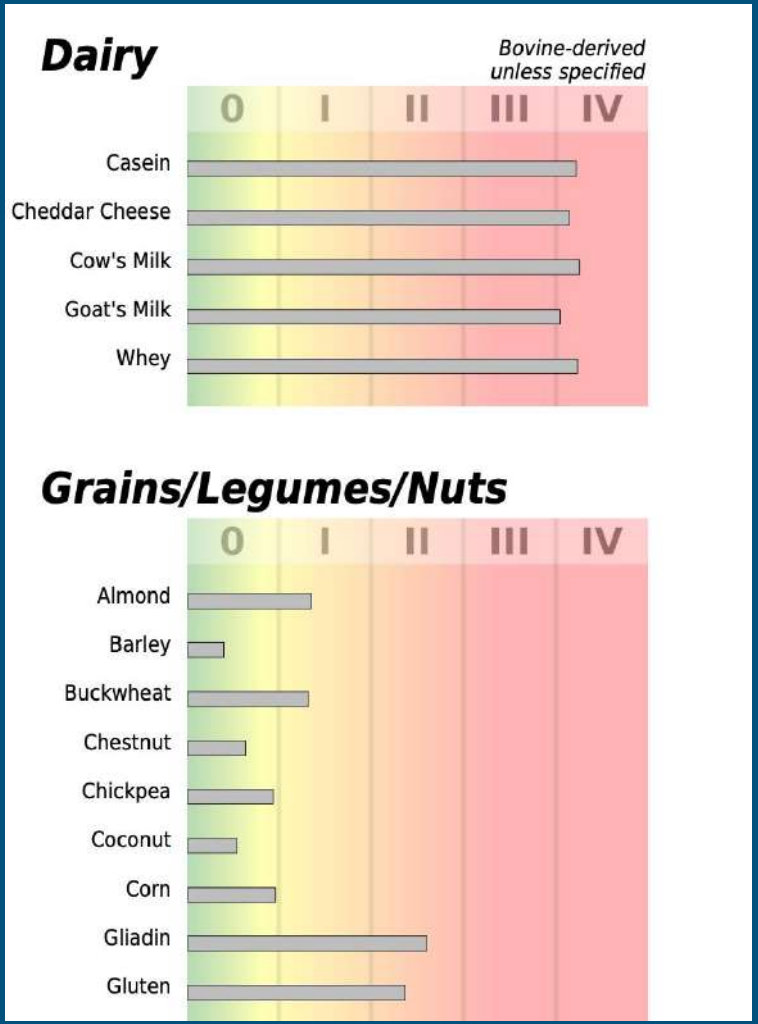
First steps

- Decongest tissues, jumpstart bowel motility: gentle detox support with milk thistle, ALA, NAC, Taurine, choline
- Calm brain quickly in PMS state: bioidentical progesterone 50 mg nightly qhs, observe tolerance and increase accordingly
- Mast cell support for brain and tissues: natural herbal mast cell stabilizer containing Quercetin, Bioflavonoids, Black Cumin, Nettles; titrate by 1 cap weekly to 2 caps twice daily
- Restart minocycline as was prescribed previously, 25 mg qd
- Order IgG food sensitivity panel and salivary adrenal assessment

Why not ketotifen for this patient? Why titrate even natural mast cell stabilizers?

ROC end of June, 2023 (quick return)

- Between visits had become immediately worse with minocycline and then experimentation with LDN, pulled these
- Was sleeping better and feeling more like herself with progesterone; intrusive thoughts only during PMS week
- Bowel movements improving
- Forgot to start natural mast cell stabilizers


Dairy
Bovine-derived unless specified
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Goat's Milk
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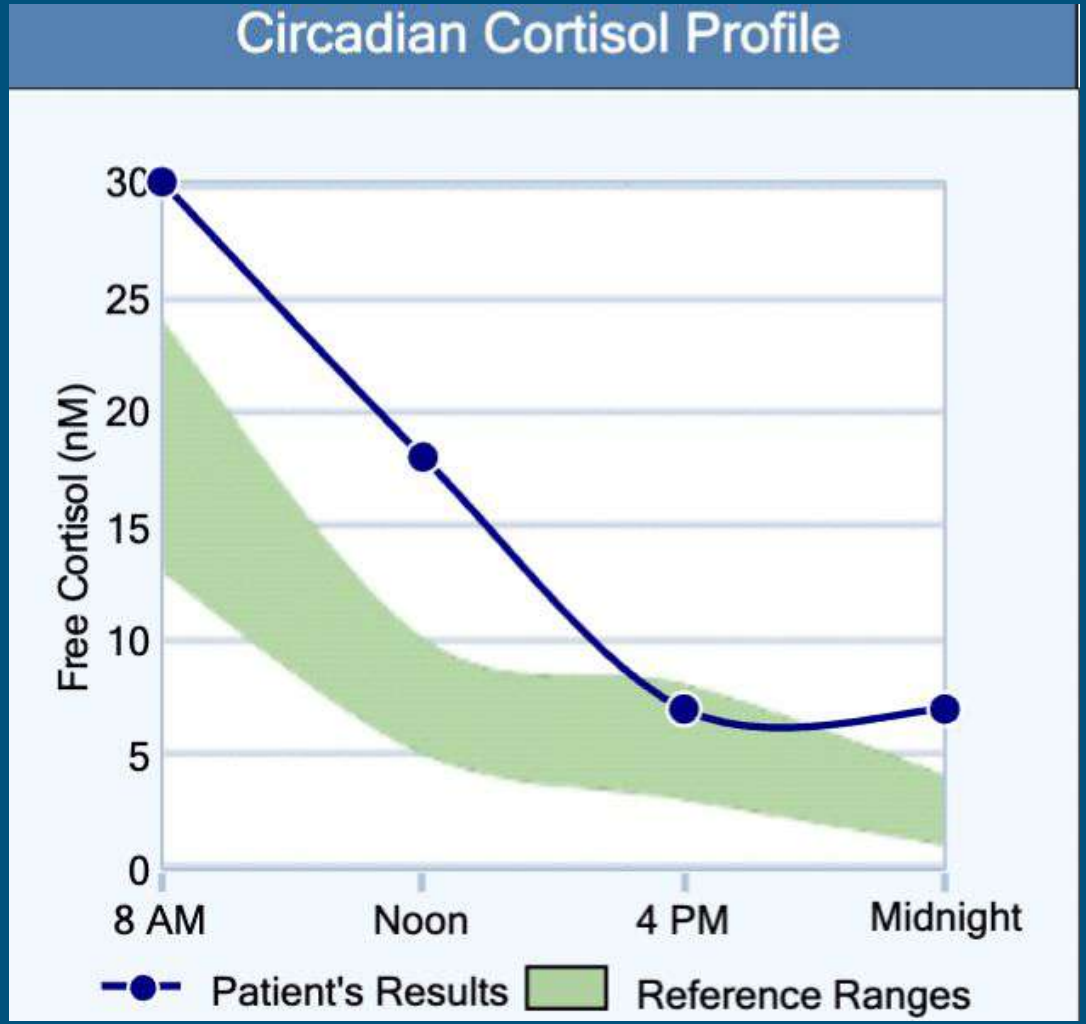
Almond
Barley
Buckwheat
Chestnut
Chickpea
Coconut
Corn
Gliadin
Gluten


Circadian Cortisol Profile
Free Cortisol (nM)
30
25
20
15
10
5
0
8 AM
Noon
4 PM
Midnight
Patient's Results
Reference Ranges

What’s up with the cortisol?
Sympathetic overdrive to support blood flow to brain?
Compensatory for inflammation?

Next steps

- Add L-theanine 200 mg at bedtime
- Up the ante on the liver support adding herbal lymphagogues in anticipation of mycotoxin test
- Start titration of natural mast cell stabilizers
- Elimination of dairy and reduction of gluten
- Add liposomal delivery herbal antimicrobial support for broad coverage of fungal and tick-borne illness issues along with mild biofilm disruption
- Increase progesterone during PMS week

September - October 2023

- Increased OCD thoughts, cramping, headaches, irregular cycles and sleep disruption with increased liver support; emergency visit necessary and moved up timeline for collection of mycotoxin panel
- Mycotoxin panel shows:
  - Aflatoxin ~10 x safe range
  - Ochratoxin 25.23 x safe range
  - MPA trace elevation
  - Citrinin 4 x safe range
- In-depth discussion of living situation reveals all furniture and air conditioners were brought from former house to current new build, there is no air exchanger, conditions are humid and they do not open the windows EVER

Next steps

- Bring the humidity level to <50%
- Get new A/C’s
- Discard moldy bed discovered after visit and anything else with visible mold
- Add food binders: chia and flax seed
- Add sauna blanket 2-3 x weekly, heating to point that a sweat is induced and replacing electrolytes afterward
- Medicated anti-fungal sinus compound, continue low dose liposomal herbal antimicrobial product

October 2023 - April 2024

- Symptoms are improving: HA stable, menses stable, sinuses stable, gut stable
- PMS symptoms are manageable, able to talk self out of intrusive thoughts
- Finally consistent with dosing in progesterone, natural mast cell stabilizer, antimicrobials, liver support, food binders and nutrition guidelines
- We add proteolytic enzymes and liposomal glutathione as I more closely connect her complaints with long-COVID
- Feeling so good that decides to:
  - Run out of progesterone and not refill
  - Pull the antimicrobials
  - Go to work as an ed-tech in her kid's school after not working for several years

June 2024 -August 2024

- HA and menses are once again stable after replacing all of the supports
- Patient has realized that she cannot work in a school
- OCD and intrusive thoughts are worse?
- We switch out mast cell stabilizer product for more direct anti-anxiety product containing adaptogens and phos serine, B6 and Mag glycinate; this does not go well, we replace the mast cell stabilizer product
- We pull the proteolytic enzymes as the tissues we are trying to access are stable, sinus pressure is visibly reduced and cognition is improving
- As we discuss hydration, she reveals that she only drinks about 16 ounces of water daily because her bladder can only hold small amounts of liquid

The psychology of inconvenient truths

Next directions for this case

- Increase anti-fungal supports based on updated mycotoxin panel (MPA increased, all others are near clear), ongoing vaginal discharge, brain fog and sugar cravings
- Gently introduce concept of trauma-directed therapy
- Re-implement non-invasive detox methods and strategic nutrition
- Ultra LDN with eye toward regeneration of healthy tissues and for layer of stability through next steps
- Continue to rehabilitate brain with POTS-directed supports