Why Mast Cell Activation?
It’s Personal
What this looked like...

- Some sort of neurologic problem
- Atypical neuropathies / paresthesias / gait disturbance
- Myopathies / myoclonus
- Atypical MS
- Some sort of atypical polycythemia
- Chronic fatigue syndrome
- Some sort of neuro / cardio syncope
- Atypical stroke type migraine +/- aura
- Stress / “Panic” reaction with anxiety & BP/HR lability
- Severe IBS-C with episodes of D
- Flushing of unknown reason
- Atypical asthma
- Sinus inflammation
- Multiple chemical sensitivity
- Breast implant reaction with severe cellulitis
- Non-immune hypothyroidism – post radiation/chemo
- Petechiae / scattered telangiectasias – often postprandial
- Herpetiform rash
- Chondritis (ear cartilage)
- Visual blurring and focus problems
- Cognitive fatigue
- Episodic vertigo
- Livido Reticularis with sun exposure
- Arthropathy
- Osteoporosis
- Globus
- Medication, food, and supplement sensitivities
- Always cold (not remediable with thyroid hormone)
- Insomnia
What the problem really was

- Gut dysbiosis, SIBO - with multiple pathogens, fungi
- Leaky gut
- Mast Cell Activation
- Neuroinflammation
- Intolerance of environmental toxins
- Stressed mitochondrial function
- Sub-optimal nutrition
Objectives

1) Participants will be able to identify neurologic, neurovascular, brain, and stress related symptoms which may potentially be mast cell activation symptoms.

2) Participants will be able to explain how mast cell activation causes mood, neurologic, and stress related symptoms, and the relationship to the gut.

3) Participants will be able to show how the mitochondria are involved with mast cells.

4) Participants will be able to implement a diagnostic plan.

5) Participants will be able to assemble the potential treatment options for mast cell activation syndrome.

Disclosures: None
Up to 17% of people in western world estimated to have mast cell activation syndrome.

That doesn’t include those with only histamine intolerance or non-MCAS over active mast cells.
## Most Common Symptoms

- Fatigue 83%
- Fibromyalgia type pain 75%
- Pre-syncope/syncope 71%
- Urticaria or pruritis 63%
- Headache (incl migraine) 63%
- Paresthesias 58%
- Nausea or vomiting 57%
- Chills 56%
- Migratory edema 56%
- Eye Irritation 53%

<table>
<thead>
<tr>
<th>Most Common Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea 53%</td>
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<td>GERD 50%</td>
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<tr>
<td>Cognitive Dysfunction 49%</td>
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<tr>
<td>Rashes 49%</td>
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<tr>
<td>Abdominal pain 48%</td>
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<tr>
<td>Throat irritation 48%</td>
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<tr>
<td>Diarrhea or Constipation 39%</td>
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<tr>
<td>Multiple drug reactions 23%</td>
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<tr>
<td>Anxiety or panic 16%</td>
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</tbody>
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Brief overview of Mast Cells

- Come from marrow CD34+ /CD117+ cells
- Mature at destination
- Found in all tissues, especially skin & barrier tissues
- Often reside around blood vessels & nerves
- Hold & release about 200 mediators
- First line responders of immune system
- Innate primarily, but also humoral
- Mediators recruit other inflammation responders
More mast cell facts

- Bind IgE via high-affinity surface receptors for IgE Fc region
- Binding not confined to IgE
- Allergic or non-allergic
- Activated by pro-inflammatory substance P
- Can activate locally or systemically
- Common cause of atopic disorders such as allergic rhinitis and allergic asthma (affects 30% of pop)

Mast Cell Disease Spectrum

Systemic Mastocytosis
– Kit D816 mutation

Monoclonal Mast Cell Activation Syndrome
– Kit mutation but does not meet SM criteria

Primary Mast Cell Activation Syndrome
– Often somatic mutations in KIT mRNA (not D816)

Secondary Mast Cell Activation Syndrome
– No mutations

Histamine Intolerance vs. MCAS

- Histamine reactions predominantly
- Absence of other MCAS mediator reactions
- Does not meet criteria for MCAS
- Could be histamine intolerance or MCA
- DAO enzyme deficiency (innate or functional)
- Histamine N-methyltransferase enzyme deficiency
Mast Cell Mediators

- Bioactive amines
  - histamine, serotonin
- Enzymes
  - tryptase, acid hydrolyzes, chymase, phospholipases
- Lipid metabolites
  - prostaglandins, leukotrienes, platelet-activating factor
- Cytokines
  - IL-1 to IL-6
- Chromogranin A
- Heparin
- Leukemia inhibitory factor
- TNF (tumor necrosis factor alpha)
- Interferon-γ
- Transforming growth factor-β
- Granulocyte-microphage colony-stimulating factor
- ATP
- Neuropeptides (vasoactive intestinal peptide (VIP))
- Growth factors (nerve growth factor- nitric oxide)
Brain Mast Cells

- Now known mast cells reside in the brain & CNS
- Serve as sensors and effectors
- Communicate between nerve, vascular, immune systems
- Able to cross the blood brain barrier, especially when BBB is compromised
- In the brain, they reside on the brain side of the BBB.
- Communicate with the brain microglia, astrocytes, and blood vessels via their mediator chemicals

Some areas of MC concentration

- **Thalamus** (relays motor & sensory to cortex)
- **Limbic system**
  - Hypothalamus (releases hormones, temp control, etc),
  - Hippocampus (motivation, emotion, learning, memory)
  - Amygdala (emotion)
- **Leptomeninges** (the inner 2 meningeal layers)
- **Choroidal plexus** (produces CSF in ventricles)
- **Area postrema** (brainstem, controls vomiting, autonomies)
- **Pineal** (produces serotonin derived melatonin)
- **Infandibulum** (connects hypothalamus & pituitary)
- **Substantia Nigra** (reward, movement)
- **Dura mater** (outer layer of spinal chord)

Hendriksen, et. al. **Mast cells in neuroinflammation and brain disorders.** Neuroscience & Behavioral Reviews. Dec 2017; 83: 774
Kempuraj D, et. al. **Mast Cell Activation in Brain Injury, Stress, and Post-traumatic Stress Disorder and Alzheimer’s Disease Pathogenesis.** Front Neurosci 2017; 11: 703
Brain mast cells interact with the microglia and glia to cause neuroinflammation
CNS Microglia

- Specialized monocytes
- Constantly surveying
- Phagocytize invaders
- Infection, toxins, chemical irritants
- Involved in neurodegenerative diseases
- Triggered by mast cells & histamine
- Involved in neuroinflammation
Mast Cell Triggers

• IgE Allergy
• Drugs, incipients
• Stress
• Infection – acute or chronic
• Inflammatory or neoplastic disease
• Exercise or physical stimuli
• Heat or cold
• Venum exposure
• And more...
Stabilize the mast cells and the microglial neuroinflammation is inhibited
White matter abnormalities are also repeatedly present in patients with systemic mast cell activation syndrome

Fig. 1: Selected punctate white matter abnormalities (see arrows) in a 55-year-old female patient with systemic mast cell activation syndrome with neurological symptoms (“fibromyalgia phenotype”).
Mast Cells & Mitochondria

- Mitochondria required for MC degranulation
- Mitochondrial DNA & ATP extruded from MC when MC degranulates
- Mt DNA then acts as an “autopathogen”
- Can travel to other areas of body


Mitochondrial STAT3 & Mast Cell Exocytosis

- OXPHOS
  - related to MC exocytosis & translocation of mitochondria to exocytosis sites upon MC activation

- STAT3
  - mitochondrial signal transducer & activator of transcription 3
  - involved in OXPHOS / ATP production

Erlick TH, et. al. Mitochondrial STAT3 plays a major role in IgE-antigen-mediated mast cell exocytosis. J Allergy Clinical Immunology. August 2014; 234(2): 460-469.e10
Mitochondrial DNA Stimulates Mast Cells and is Inhibited by Luteolin

Asadi S, Theoharides TC. Corticotropin-releasing hormone and extracellular mitochondria augment IgE-stimulated human mast-cell vascular endothelial growth factor release, which is inhibited by luteolin. Journal of Neuroinflammation. 9, 85(2012)
Migraine & Pain
The MC Pain Connection

- MC mediators impact central, spinal and enteric neurons
- Activated by stress
- Sensitize nerve terminals
- Many contributors & feedback loops
- Tryptase, CGRP, PAR2, Substance P
- Migraine, peripheral pain, fibromyalgia
The Pain Stress Connection

Stress

HPA

Increased CRF

MC infiltration & activation

Sensitization of Nerve Terminals
Migraine

- Sensory nerves & meningeal mast cells communicate via “couplings”
- Interact with CNS & immune system
- Meningeal neuroinflammation (neuropeptide release, vasodilation, plasma protein extravasation, mast cell degranulation)
- Leads to trigeminal nocioceptor sensitization

- Mast cells reside in the meninges (dura mater)
- MC an intermediate between triggers & activation of meningeal nocioceptors
- Mast cells & sensory neurons – both the source and target of neuropeptides

Sensory Nerve Response to Noxious Stimuli

Peripheral Sensory Nerve Cells (Nociceptors)

Stimulus

Spinal Cord Dorsal Root Ganglia Afferent Fibers (to brain)

Cleavage & Activation by Tryptase

PAR2

sensitization of TRPV1, TRPA1

Active PAR2

Peripheral SP, CGRP & Neuroinflammation
(Pain, neuronal excitability, & visceral hyperalgesia)

Similar process in trigeminal sensory afferents


Amadesi S, et. al. Protease-activated receptor 2 sensitizes TRPV1 by protein kinase C epsilon and A-dependent mechanism in rats and mice. J. Physiol. 575(Pt 2), 555-571
Pain: Peripheral & Migraine

- CGRP & Substance P are adjacent to mast cells (central & peripheral)
- Perpetuate neurogenic inflammation by further release of both

Meningial Nocioceptors → Release → CGRP (Calcitonin Gene-Related Peptide) → Activates Histamine

Histamine → Releases CGRP & Substance P (Neurotransmitters)

Mechanosensitive C-Fibers

CGRP & Substance P are adjacent to mast cells (central & peripheral) and perpetuate neurogenic inflammation by further release of both.
Migraine & Flushing

• PACAP type migraine

• Pituitary adenylate cyclase activating peptide1-38 triggers migraine

• Flushing thought due to MC degranulation

• PACAP1-38 known to degranulate both peritoneal and dural mast cells

Fibromyalgia Proposed Central Pain Path

- Muscle pain, cognitive dysfunction, fatigue, sleep disturbance
- Reduced pain tolerance

Thalamic Mast Cells → Histamine, Tryptase, IL-6 → HK-1, Subst P, TNF, CRH

Thalamic Microglia → Direct mediation → Neurosensitization via either:

Microglia in Ascending Nocioceptive tracts in Spinal cord

A Mast-Cell-Specific Receptor Mediates Neurogenic Inflammation and Pain

Dustin P. Green • Nathachit Limjunyawong • Naina Gour • Priyanka Pundir • Xinzhong Dong

Highlights

• The mast cell receptor Mrgrpb2 is required for neurogenic inflammatory pain

• Substance P (SP) recruits immune cells via Mrgrpb2 independent of the NK-1 receptor

• SP activation of Mrgrpb2 and its human ortholog MRGPRX2 releases cytokines

• Mrgrpb2/X2 is a target for treating pain
Mood & Psychologic Disorders
Mast Cells & Neuro-Psychiatry

• MCAS (as opposed to mastocytosis)

• Neurologic and/or psychiatric symptoms

• No unifying underlying cause

• Can be multiple heterogenous symptoms

• Empiric therapy often unsatisfactory

• "Multisystem polymorbidity of generally inflammatory +/- allergic themes."

Common mastocytosis symptoms

- 33% of mastocytosis presented with neuropsychiatric symptoms
- Fatigue, musculoskeletal
- Chronic headache 35% (migraine 37.5%, aura 66%). Often with other symptoms: flushing, pruritis, etc.
- Depression-anxiety 40-60%
- Cognitive impairment 38.6%
- Syncope 5%, acute back pain 4%, MS findings on radiology 1%

Depression, Anxiety, Fatigue

• Most work done in mastocytosis. 3 studies:

• Depression 64% (psychic anxiety, depressed mood/work/interests. Masitinib improved in 67% of those.

• Negative emotionality: depression (78.9%) & perceived stress (42.1%). Brain mast cells located in diencephalon (emotion).

• Fatigue in 7 patients. Triggers of heat/cold, exercise, food, ETOH, psychological stress. VAS 80 during attacks and 40 between attacks. Impacted social & recreational activities in 7/7 and occupational activity in 6/7.

Evidence for Cognitive Impairment in Mastocytosis: Prevalence, Features and Correlations to Depression

Daniela Silva Moura, Serge Sultan, Sophie Georin-Lavialle, Stéphane Barete, Olivier Lortholary, Raphael Gaillard, Olivier Hermine

Published: June 20, 2012 • https://doi.org/10.1371/journal.pone.0039468

controlled for all patients. Patients with mastocytosis presented high levels of cognitive impairment (memory and/or attention) (n=22; 38.6%). Cognitive impairment was moderate in 59% of the cases, concerned immediate auditory (41%) and working memory (73%) and was not associated to depression (p≥0.717). In conclusion, immediate auditory memory and attention impairment in mastocytosis are frequent, even in young individuals, and are not consecutive to depression. In mastocytosis, cognitive complaints call for complex neuropsychological assessment. Mild-moderate cognitive impairment and depression constitute two specific but somewhat independent syndromes in mastocytosis. These results suggest differential effects of mast-cell activity in the brain, on systems involved in emotionality and in cognition.
Neurologist Consults

- Presentation to Mayo Clinic neurology
- Headache 35%, syncope, vertebral compression fracture (MC infiltration), multiple sclerosis (also with mastocytosis)
- Actually mastocytosis
- Mastocytosis may mimic neuro presentations, especially if flushing, abdominal cramping, diarrhea are present.

Stress
Stress & mast cells

• Mast cells involved in a variety of neuroinflammatory diseases.

• Especially if those conditions already are potentially worsened by stress.

• Not activated by IgE at Fc receptors, but rather by other immunoglobulins, anaphylatoxins, neuropeptides and cytokines.

• Do not see allergic degranulation in these cases.

Stress, Mast Cells & BBB

• Usually stress activates HPA axis by release of corticotropin releasing hormone (CRH). Glucocorticoids then down-regulate immune responses.

• But, acute stress can be proinflammatory and mediated by activated mast cells.

• The BBB barrier sees increased permeability with stress and this is inhibited by giving disodium cromoglycate, a mast cell stabilizer.

• After blocking the CRH-receptor with Antalarmin, less BBB permeability is seen.

• Injecting CRH into the hypothalamic paraventricular nucleus (PVN) mimics acute stress which is blocked by pretreatment with cromolyn.

• Also, in W/Wv mast cell-deficient mice, stress does not disrupt the BBB in the diencephalon and cerebellum.

• Therefore the BBB is regulated by CRH and mast cells, and possibly, brain inflammatory disorders exacerbated by acute stress as well.

Proposed that CRF1 is a modulator for both immunologic and psychologic stress.
Stress, neuroinflammation & neurodegeneration

• Stress induces release of CRH (corticotropin-releasing hormone) form paraventricular nucleus of hypothalamus.

• Activates glia and mast cells via CRH receptors.

• Releases neuroinflammatory mediators. Also induces proinflammatory mediator release in the periphery promoting neuroinflammation.

• Mast cell activation in brain injury, stress, PTSD may increase neuroinflammatory and neurodegenerative disease pathogenesis.

Mast cells & gut permeability

- CRF causes Intestinal Epithelial Barrier Injury and increased permeability
- Response to MC proteases and TNF-alpha
- Multiple feedback loops with MC mediators


Many Types of Stressors

• Emotional
• Physical
• Chronic infection or illness
• Environmental toxins
• Oxidative stress
Alzheimer’s

• Amyloid-ß protein accumulation promotes overactivation & recruitment of microglia, which penetrate plaques and leads to production of pro-inflammatory and cytotoxic molecules

• Both microglia & mast cells found surrounding amyloid plaques in AZ patients at autopsy

• Proposed that mast cells are either attracted to the sites by glia or are first responders

TBI

• TBI contributes to Alzheimer's disease by promoting chronic neuroinflammation and neuronal death.

• At the time of injury, mast cells recruit immune cells to the site via release of mediators across the BBB.

• In combination with risk factors, this leads to neurodegeneration and AD.

Activated brain mast cells contribute to postoperative cognitive dysfunction by evoking microglia activation and neuronal apoptosis

Xiang Zhang, Hongquan Dong, Nana Li, Susu Zhang, Jie Sun, Shu Zhang & Yanning Qian

Journal of Neuroinflammation 13, Article number: 127 (2016) | Download Citation

Tibial fracture surgery induced MCs degranulation, microglia activation, and inflammatory factors production, which initiated the acute brain inflammatory response and neuronal death and exhibited cognitive deficit. Site-directed preinjection of the “MCs stabilizer” disodium cromoglycate (Cromolyn) inhibited this effect, including decrease of inflammatory cytokines, reduced MCs degranulation, microglia activation, neuronal death, and improved cognitive function 24 h after the surgery. In vitro study, we found that the conditioned medium from lipopolysaccharide (LPS)-stimulated mast cells line (P815) could induce primary microglia activation through mitogen-activated protein kinase (MAPK) pathway signaling and subsequent production of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). In addition, the activated P815 could directly induce neuronal apoptosis and synapse injury with microglia independently. Cromolyn could inhibit P815 activation following improved microglia activation and neuronal loss.
Multiple Sclerosis
Multiple Sclerosis

- Mast cells at sites of inflammatory demyelination
- Mast cell tryptase seen elevated in cerebrospinal fluid
- Secreted histamine promotes edema
- Secreted proteases cause demyelination
- Theory that MS relapses and remits following mast cell degranulation and restoration of stored contents.
- Theory that mast cells originally amplify in the brain during a remote or childhood infection

Experimental allergic encephalomyelitis (EAE) model with human counterpart as multiple sclerosis

Both EAE and MS considered CD4+ T cell-mediated autoimmune diseases affect CNS

Shown that in EAE mast cell-deficient mice show significantly reduced disease incidence vs wild type.

Restoring mast cells in the deficient mice induces early severe disease.

Suggests mast cells are critical for full disease manifestation
Stroke
Stroke

- Cerebral ischemia brain injury triggers many types of inflammatory cell recruitment.

- Mast cells reside in the brain and meninges. Are first responders (even prior to microglia) to ischemia and hemorrhage.

- Act first to release vasoactive and neuroactive mediators from preformed cytoplasmic granules.

- Contribute to BBB damage, brain edema, prolonged extravasation, hemorrhage. Act on the basal membrane.

- Contribute to continued BBB damage > infiltration of other signals and blood-borne cells.

Parkinson’s
Parkinson’s

• Found that histamine triggers microglial phagocytosis via H1R histamine receptor activation and ROS production via both H1R and H4R activation.

• Performed in Substantia Nigra.

• Substantia nigra particularly susceptible to microglial activation, and histamine in particular.

• Others found that when the secretions of microglial cells were exposed to histamine, degeneration of the dopaminergic neurons was seen.

Rocha SM, et al. Histamine induces microglia activation and dopaminergic neuronal toxicity via H1 receptor activation. Journal of Neuroinflammation. 04 June 2016. 13(137)
Inflammatory mediators resulting from transglutaminase 2 expressed in mast cells contribute to the development of Parkinson's disease in a mouse model

Gwani Ui Hong, Jin Whan Cho, Soo Youl Kim, Joo Ho Shin, Jai Youl Ro

Highlights

- Mast cells recruited into substantia nigra (SN) of PD, are activated by MPP⁺.

- The activated mast cells activate TG2 in the SN tissues of PD model in mice.

- Mast cells-activated TG2 releases mediators such as histamine, LTs and cytokines.

- Mediators may induce neuroinflammation caused DA neuron death in mouse and human PD.

- TG2 inhibitor may be developed as a therapeutic agent for human PD patients.
POTS & Ehlers Danlos

• Pilot study. Only 15 patients

• Ehlers Danlos Syndrome patients and 80% with known diagnosis of Postural Orthostatic Tachycardia Syndrome.

• Goal was to determine if patients with EDS and POTS also have mast cell activation as a phenotype

• 6 of the 9 (66%) patients with a dual diagnosis of EDS and POTS had validated symptoms of a mast cell disorder suggestive of MCAS

For your reading pleasure...

Gut Brain:


Permeability:

- Groschwitz K, et. al. Mast cells regulate homeostatic intestinal epithelial migration and barrier function by a chymase/Mcpt4-dependent mechanism. *PNAS.* December 29, 2009; 106(52):22381-22386

Permeability bacterial translocation / LPS endotoxemia


Celiac & Lectins:

- Barbosa-Lorenzi VC, et. al. The lectin ArtinM binds to mast cells inducing cell activation and mediator release. *Bioch Biophys Res Communications.* 16 Dec 2011; 416(3-4): 318-324
- Moreno AN, et. al. Mast cell degranulation induced by lectins: effect on neutrophil recruitment. *Int Arch Allergy Immunol.* 2003 Nov; 132(3): 221-30
Be looking for overlapping symptoms that could represent mast cell activation
Systemic Mastocytosis diagnostic criteria

- Major + at least 1 minor, or only 3 minor criteria

- Major
  - Multifocal aggregates of ≥ 15 mast cells in a noncutaneous tissue biopsy specimen

- Minor
  - Aberrant mast cell morphology
  - Aberrant CD25 and/or CD2 expression
  - Codon 816 KIT mutation
  - Serum baseline tryptase >20 or 2x baseline +2

1º vs 2º vs Idopathic MCAS

• Primary (clonal MCAS)
  – KIT D816V. Usually CD25 in mast cells
  – A) with confirmed mastocytosis (CM or SM)
  – B) with just 2 minor SM criteria

• Secondary
  – No KIT D816V or neoplastic MC
  – IgE-mediated allergy, other hypersensitivity disease, or immunologic disease causing MCA

• Idiopathic
  – Meets MCAS criteria, but no related reactive disease, or IgE-dependent allergy, or neoplastic/monoclonal MC.
MCAS Consensus Criteria

• Valent criteria. MCAS diagnosis requires all three

• Criterion A
  – Clinical signs of MCA that are severe and recurrent (i.e., anaphylaxis, flushing, pruritis, urticaria, angioedema, nasal congestion or pruritis, wheezing, throat swelling, headache, hypotension, diarrhea, etc) in at least 2 organ systems

• Criterion B
  – Positive markers. Tryptase increase of 20% + 2 ng/mL

• Criterion C
  – Response to therapy with MC-stabilizing or MC-mediator inhibiting/blocking drugs.
Workup

- Tryptase (best while flared)
- Histamine, Heparin, Chromogranin A, Prostaglandin D2 (PGD2)
- CBC w/differential, serum chemistries
- Quantitative immunoglobulins (if frequent/chronic infection or poor healing)
- PT/PTT if easy bruising/bleeding or thromboembolic events
- Spot urine PGD2
- 24 hr urine PGD2 or 2,3-dinor-11-ß-prostaglandin F2a
- 24 hr urine N-methylhistamine
- 24 hr urine LTE4


Usefulness of markers

- sChromogranin A 49%
- pHistamine 49%
- pHeparin 48%
- pPGD2 46%
- 24u PGD2 44%
- Ru PGD2 26%
- 24u N-MH 11%
- Ru N-MH 7%

Mast Cell activity can affect multiple systems whether it meets MCAS criteria or not.

And it’s modifiable.
Drug Treatments

- H1 histamine receptor agonist (anti-histamines)
- H2 histamine receptor agonist (acid blockers)
- Leukotriene inhibitors
- Cromolyn – Mast cell stabilizer – nasal, oral
- Aspirin, NSAIDS – prostaglandin inhibitors
- Glucocorticoids

- Omalizumab
- Cytoreductive agents – IFN-a, cladribine
- Multikinase inhibitor – Midostaurine
- Tyrosine kinase inhibitor - Masitinib
Potential Problems

• H1 Blocking Anti-histamine
  – Diphenhydramine (Benedryl)
  – anti-cholinergic dementia / Alzheimer’s risk
  – Less risk with non-sedating Loratadine, Cetirizine

• H2 Blocking Anti-histamine
  – Ranitidine, Famotidine
  – Acid inhibition and dysbiosis / SIBO

• Aspirin, NSAIDS
  – Bleeding, kidney
Nutritional Supplements

- Quercetin – MC stabilizer
- Luteolin (+/- with Rutin) – MC stabilizer
- Butyrate – MC Stabilizer
- DAO enzyme – intestinal histamine degradation enzyme
- Support Histamine N-methyltransferase methylation


Other Natural MC stabilizers & anti-histamines

- Flavonoids
- Phenols – ie Curcumin
- Theanine
- Coumarins
- Ellagic acid
- Terpenoids
- Vitamin C (DAO enzyme co-factor)


Histamine N-methyltransferase

- Systemic histamine degradation enzyme
- Methylates Histamine using SAMe to form N-methylhistamine
- Support methylation pathways, including with TMG (Betaine).
Cheryl

- 51 y/o woman
- C/o bloating, constipation, slow digestion, heartburn
- High anxiety with depression many years, worsening
- Emotional lability, cognitive dysfunction/brain fog, severe social anxiety
- Multiple failed antidepressants, anxiolytics
- Flushing after eating: face & chest, for 1 year
- Tryptase 2x normal (20.1 ng/mL), Kit D816V negative
- Histamine borderline high
- Breath test – flat line H2 and low methane
- Stool tests – low bacteria except Bacteroidetes, low sIgA, high Beta-glucuronidase, low Akkermansia, low butyrate, neg mycology/parasites
- Quercetin, Luteolin, DAO enzyme, Butyrate, trial of Loratidine
- Nystatin, Intestinal motility agents
- Low histamine, anti-inflam, MC stabilizing diet
- N-acetylglucosamine, Ca D-glucarate, digestive enzymes
- Spore probiotic, B infantis / low histamine probiotics
- Gradual fiber and resistant starches as tolerated
Avoid & Address Triggers

- Gut dysbiosis, SIBO, Parasites
- Gut permeability
- Stress
- Chronic infections, Lyme
- Environmental Triggers – chemicals, mold
- Oxidative Stress
- Mitochondrial dysfunction
Let Food
Be Your Medicine
# High Quercetin Foods (mg/100gm)

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<th>Product</th>
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<td>Okra, raw</td>
<td>20.97</td>
</tr>
<tr>
<td>Spring onion leaves, red</td>
<td>12.60</td>
</tr>
<tr>
<td>Onions, cooked</td>
<td>24.36</td>
</tr>
<tr>
<td>Onions, raw</td>
<td>21.40</td>
</tr>
<tr>
<td>Onions, spring, red</td>
<td>30.60</td>
</tr>
<tr>
<td>Onions, red, raw</td>
<td>31.77</td>
</tr>
<tr>
<td>Peppers, hot chili</td>
<td>14.70</td>
</tr>
<tr>
<td>Peppers, long yellow</td>
<td>10.36</td>
</tr>
<tr>
<td>Peppers, sweet green</td>
<td>2.21</td>
</tr>
<tr>
<td>Radicchio</td>
<td>31.51</td>
</tr>
<tr>
<td>Radish leaves, raw</td>
<td>70.37</td>
</tr>
<tr>
<td>Rocket, wild, raw</td>
<td>66.19</td>
</tr>
<tr>
<td>Scallions</td>
<td>10.68</td>
</tr>
<tr>
<td>Sweet potato leaves</td>
<td>9.83</td>
</tr>
<tr>
<td>Tomato puree</td>
<td>4.12</td>
</tr>
<tr>
<td>Turmeric</td>
<td>4.92</td>
</tr>
<tr>
<td>Watercress, raw</td>
<td>29.99</td>
</tr>
<tr>
<td>Chia seeds</td>
<td>18.42</td>
</tr>
<tr>
<td>Green tea, brewed</td>
<td>2.49</td>
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<tr>
<td>Carob flour</td>
<td>38.78</td>
</tr>
<tr>
<td>Bee pollen</td>
<td>20.95</td>
</tr>
<tr>
<td>Cocoa, dry powder</td>
<td>3.37</td>
</tr>
<tr>
<td>Buckwheat, whole</td>
<td>15.38</td>
</tr>
</tbody>
</table>
High Luteolin Foods (mg/100gm)

- Oregano (Mexican) dried  1028.75
- Peppermint, fresh  11.3
- Sage, fresh 16.70
- Celery seed  811.41
- Parsley, dried  19.75
- Thyme, fresh  45.25
- Juniper berries, ripe  69.05
- Celery hearts, green  3.50
- Chinese celery, raw  34.87
- Chicory greens, raw  2.08
- Lettuce red leaf  2.50
- Radicchio  37.98
Nutrient Rich Diet

• Plant rich
• Includes greens, colors, sulfurs
• Anti-oxidant rich
• Anti-inflammatory
• Olive oil
• Fiber rich
• Quality proteins
• Supports mitochondria
• Supports detoxification and hormonal systems
• Consider gluten free and lower lectin

Penissi AB. Regulation of Immune and Nonimmune Mast Cell Activation by Phenols from Olive Oil. March 12, 2019, Technological Innnovation in the Olive Oil Production Chain. DOI: 10.5772/intechopen.84595

Reduce High Histamine Foods

Aged cheese
Alcohol
Beans
Cashews
Chili powder
Chocolates
Cinnamon
Cloves
Cocoa
Eggplant

Fermented foods
Fruits (dried)
Fruits
(avocado, citrus, pineapple, strawberry, papaya)
Legumes
Pickled foods
Smoked or processed meat

Fish or meat not extremely fresh
Vegetables
(mushroom eggplant, tomato, spinach)
Soy Sauce
Vinegar
Walnuts
<table>
<thead>
<tr>
<th>Foods</th>
<th>Gut Conditions</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Alcohol</td>
<td>- Dysbiosis</td>
<td>- NSAIDS</td>
</tr>
<tr>
<td>- Raw egg white</td>
<td>- Leaky gut</td>
<td>- Antidepressants</td>
</tr>
<tr>
<td>- Tea (green, black, or</td>
<td>- Celiac</td>
<td>- SSRIs</td>
</tr>
<tr>
<td>mate)</td>
<td>- IBD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genetic mutations</td>
<td>- Cardiac rhythm medications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(β-blockers, calcium channel blockers)</td>
</tr>
</tbody>
</table>
Histamine producing probiotics

- Lactobacillus acidophilus
- Lactobacillus casei
- Lactobacillus reuteri
- Lactobacillus helveticus
- Lactobacillus lactis
- Lactobacillus delbrueckii
- Lactobacillus bulgaricus
Histamine Degrading Probiotics

- Lactobacillus rhamnossis
- Lactobacillus salivarius
- Lactobacillus gasseri
- Lactobacillus plantarum
- Bifidobacter infantis/longum
- Bifidobacter lactis
- Bifidobacter bifidum
- Bacillus coagulans (Lactobacillus sporogenes)
Provide Nutritional Support

- Methylation
- Detoxification
- Mitochondria
- Hormonal
- Microbiome
Situations to be looking for Mast Cell Activation or Histamine Intolerance

- Mood disorders
- Neurologic conditions
- Cognitive decline
- Neurodegenerative conditions
- Stress & PTSD
- Fatigue /chronic fatigue syndrome
- IBS, gut dysbiosis/SIBO, GERD, Nausea
CHOOSE JOY