Mast Cell Instability - Why It Matters

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Patients, Clinicians and Symptoms

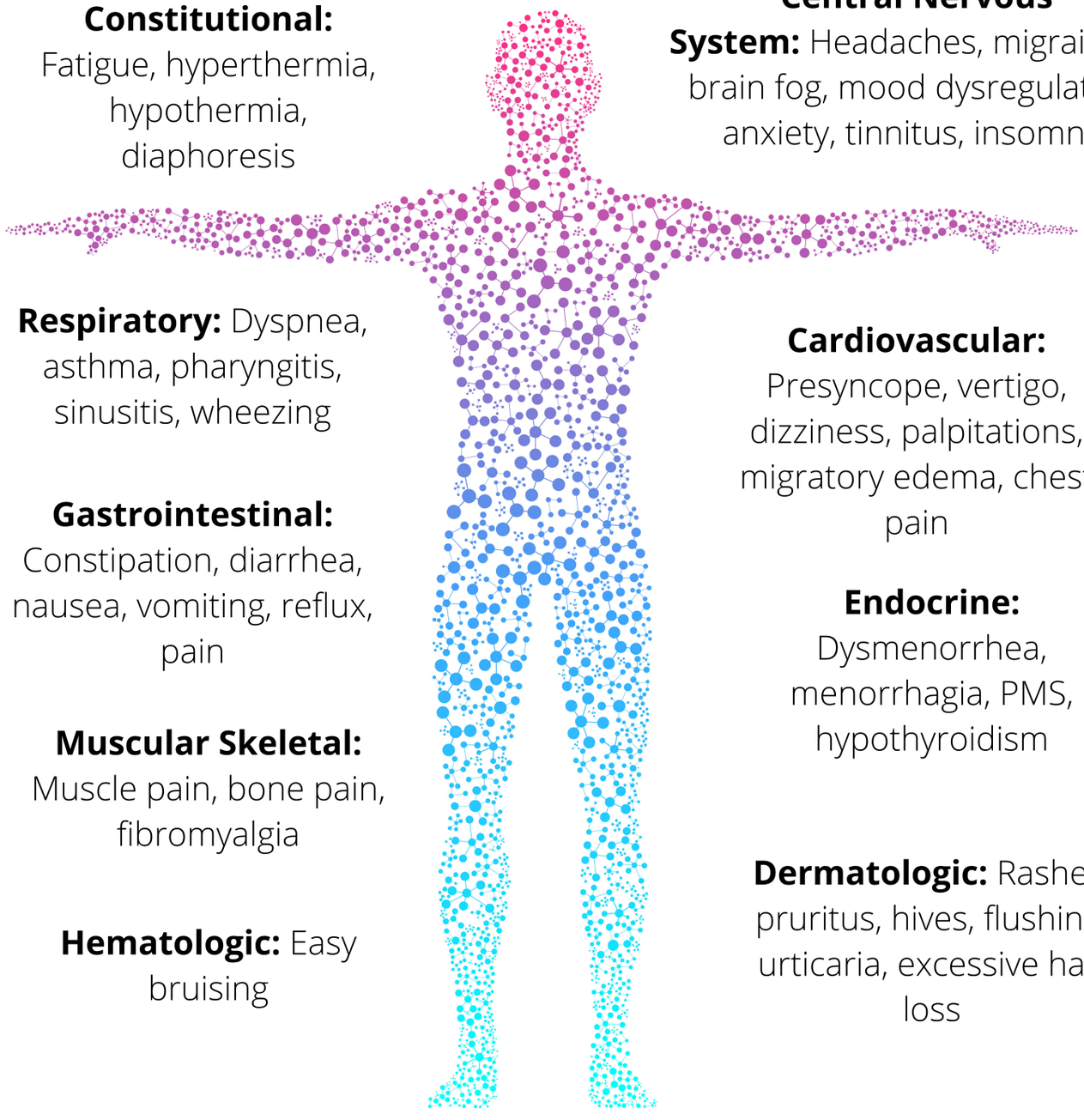
Patients, Clinicians and Symptoms

- We hear about and try to manage nonspecific, chronic symptoms every day:
  - Fatigue
  - Digestive complaints
  - Headaches
  - Pain
  - Pruritus and rashes
  - Brain fog
  - Anxiety
- They are multi-system
- Perhaps part of defined illness, often “idiopathic”
- An inflammatory component; perhaps an allergy history
- What unifies them - pathophysiologically?

Symptoms by System

Constitutional:
Fatigue, hyperthermia, hypothermia, diaphoresis

Central Nervous System: Headaches, migraines, brain fog, mood dysregulation, anxiety, tinnitus, insomnia



Respiratory: Dyspnea, asthma, pharyngitis, sinusitis, wheezing

Cardiovascular: Presyncope, vertigo, dizziness, palpitations, migratory edema, chest pain

Gastrointestinal: Constipation, diarrhea, nausea, vomiting, reflux, pain

Endocrine: Dysmenorrhea, menorrhagia, PMS, hypothyroidism

Muscular Skeletal: Muscle pain, bone pain, fibromyalgia

Dermatologic: Rashes, pruritus, hives, flushing, urticaria, excessive hair loss

Hematologic: Easy bruising

Patients, Clinicians and Diseases

Patients, Clinicians and Diseases

- We diagnose and treat chronic, inflammatory illness every day:
  - Dermatitis
  - Asthma
  - IBD or IBS
  - Arthritis
  - Psoriasis
  - ASD
  - CFS
  - Fibromyalgia
- Many of our patients have been suffering for years or decades, seen multiple providers, and often received multiple diagnoses - again, often “idiopathic”
- Is there a common thread?

What Are Mast Cells: Biology

What Are Mast Cells: Biology

- Immature MCs arise in bone marrow
- Complete maturation peripherally
    - on the influence of local residing microenvironment, which defines their phenotype and, consequently, their function
- White adipose tissue, too, is a MC progenitor reservoir
- Ultimately site (sparsely) in all tissues
    - Preferentially located at **environmental interfaces** [skin, lungs, intestines] and lymphovascular tissue; migrate to mucosal and connective tissues
    - Optimally positioned to serve as **sentinels of adverse environmental change**

Traina G. **Mast Cells in Gut and Brain and Their Potential Role as an Emerging Therapeutic Target for Neural Diseases**. Front Cell Neurosci. 2019 Jul 30;13:345. doi: 10.3389/fncel.2019.00345. PMID: 31417365; PMCID: PMC6682652.

Lawrence B. Afrin, Joseph H. Butterfield, Martin Raithel & Gerhard J. Molderings (2016) **Often seen, rarely recognized: mast cell activation disease – a guide to diagnosis and therapeutic options**, Annals of Medicine, 48:3, 190-201, DOI: 10.3109/07853890.2016.1161231

What Are Mast Cells: Biology

- MCs **secrete pre-stored mediators and synthesize *de novo* mediators** in response to allergic, microbial, and non-immune triggers
- Collectively MCs express **more than 200 mediators** [histamine, prostaglandins, tryptase] each with many effects

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What Are Mast Cells: Biology

- MCs are immune effectors and regulators, central in innate and adaptive immunity
- Apart from critical involvement in allergy, MC mediators critically guide development, and maintain integrity/function, in all tissues
- MCs regulate host defense by acting as innate immune cells; and recruit other immune cells
- MCs **induce/regulate inflammation**

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What Are Mast Cells: Biology

- MCs orchestrate **microbial, toxic, and physical environmental defense** through classic non-selective degranulation, and selective mediator release ("piecemeal" or "differential" degranulation)
- MCs also aid wound healing, tissue remodeling, and degrading certain endogenous toxins in bacterial infection
- **The fine regulation of these mechanisms infers potential for diverse havoc from dysregulated MCs**

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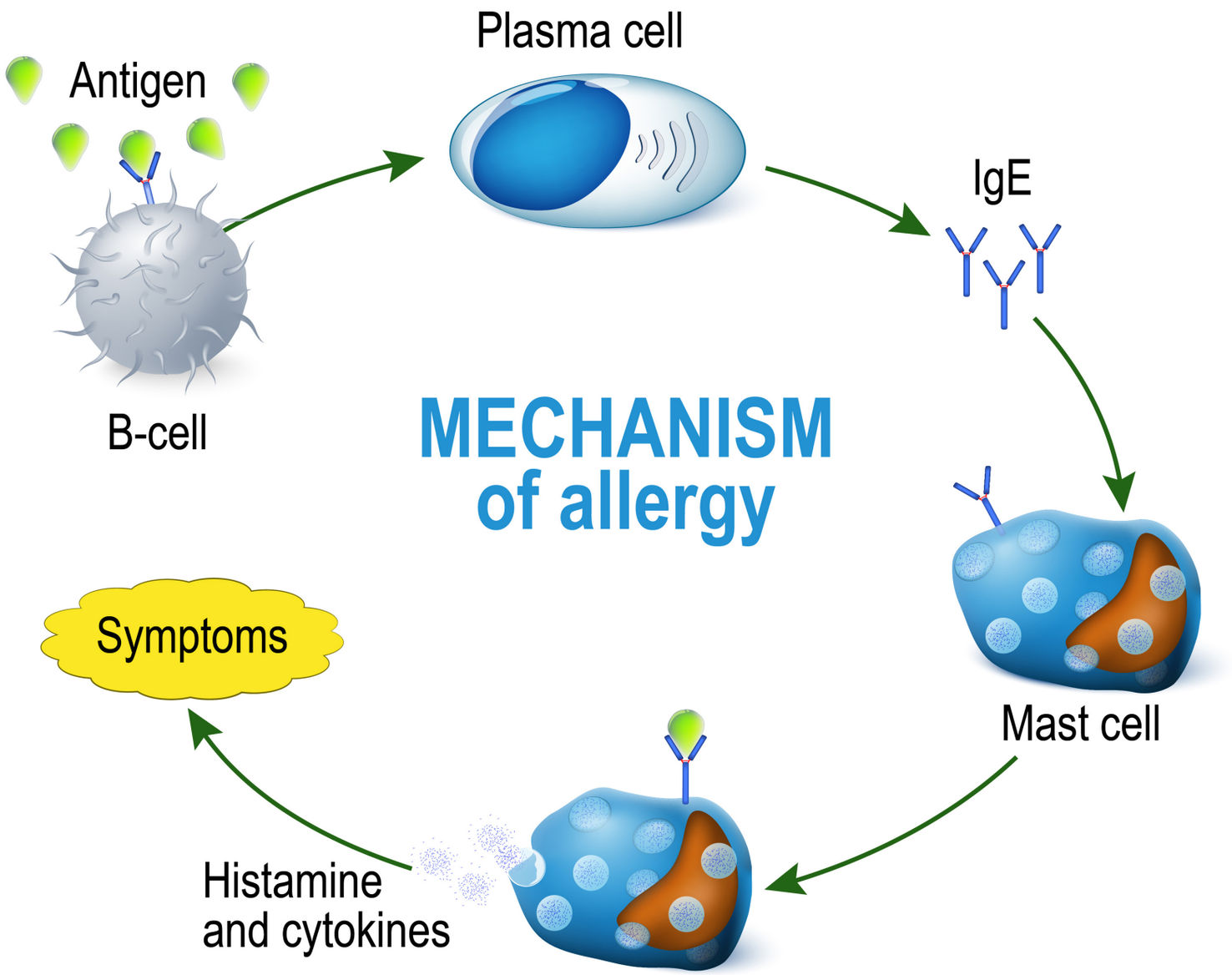
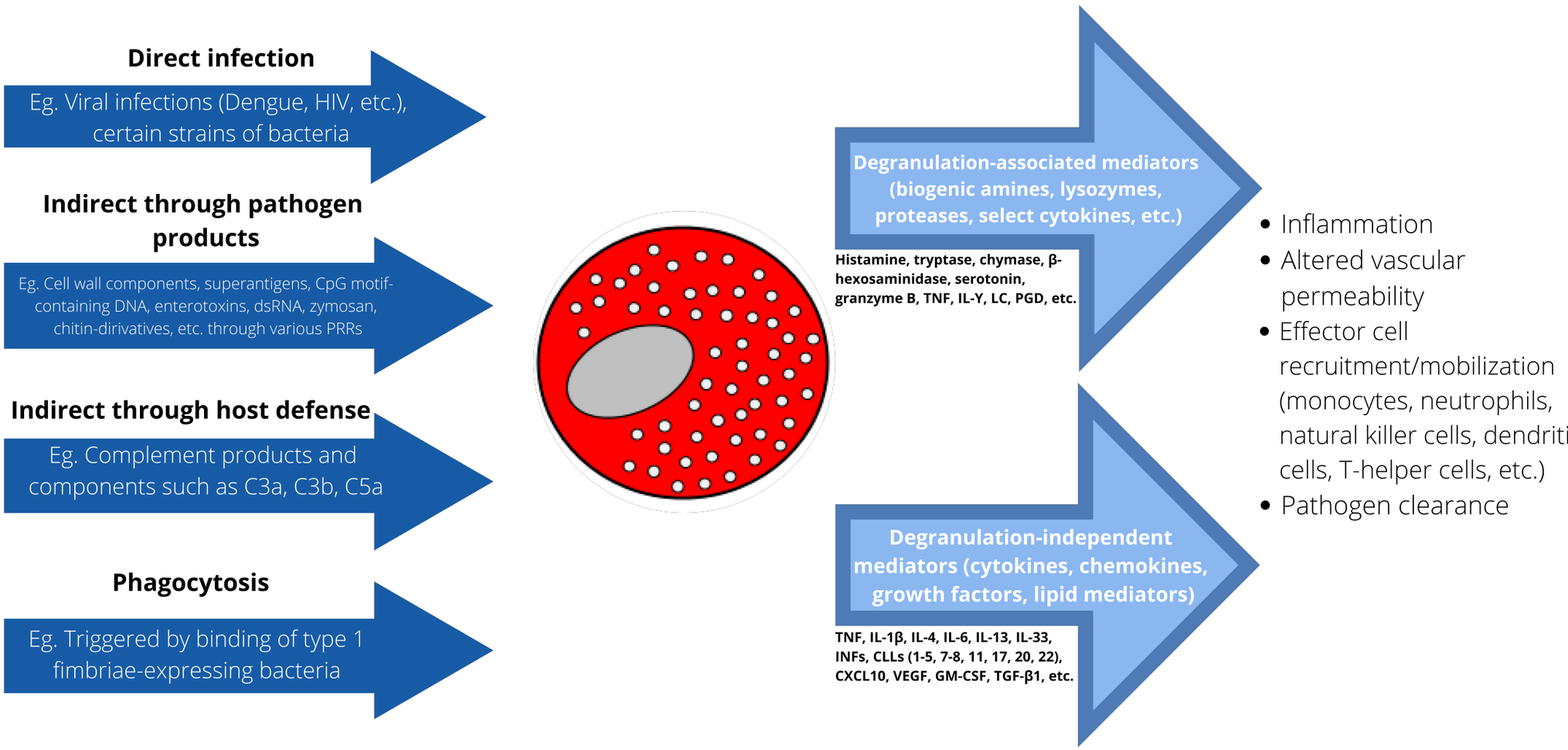
Mast Cells and Mechanism of Allergies



Pathogen Response



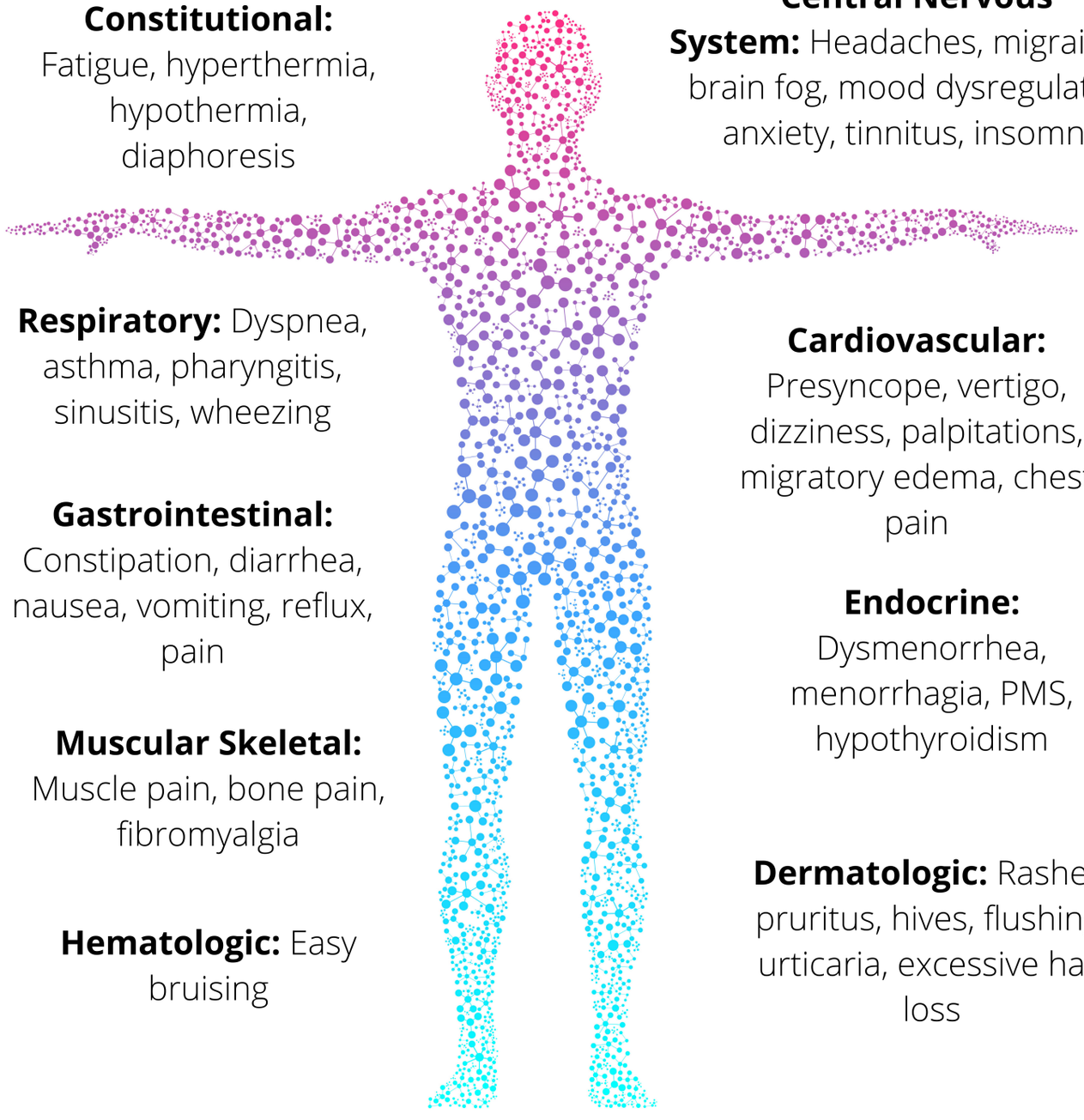
Mast cells can recognize and **respond to pathogens** either directly through pathogen infection, or indirectly through an array of pathogen products, host defense mechanisms, or phagocytosis. Activation results in the secretion of classical mast cell mediators that can be categorized as degranulation-dependent or degranulation-independent. These **mediators contribute to the inflammation** and changes to the site of pathogen infections, recruitment of other immune cell types, and regulation of the immune response to pathogens.

Marshall JS, Portales-Cervantes L, Leong E. **Mast Cell Responses to Viruses and Pathogen Products**. *Int J Mol Sci*. 2019;20(17):4241. Published 2019 Aug 30. doi:10.3390/ijms20174241

Mast Cell Symptoms by System

Constitutional: Fatigue, hyperthermia, hypothermia, diaphoresis

Central Nervous System: Headaches, migraines, brain fog, mood dysregulation, anxiety, tinnitus, insomnia



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Dermatologic: Rashes, pruritus, hives, flushing, urticaria, excessive hair loss

Hematologic: Easy bruising

Mast Cell Symptoms by Prevalence

Fatigue	83%
MCAS-driven musculoskeletal pain	75%
Presyncope (lightheadedness, weakness, dizziness, vertigo) and/or syncope	71%
Pruritus	63%
Headache, especially migraine	63%
Peripheral (usually distal) sensory and/or motor neuropathies inc paresthesias	58%
Nausea or vomiting	57%
Hypothermia	56%
Migratory edema	56%
Irritated (often described as “dry”) eyes	53%
Dyspnea (often low-grade, inconstant)	53%
GERD (often treatment-refractory)	50%
Memory, concentration, word-finding difficulties; other cognitive dysfunction	49%
Rashes	49%
Pharyngitis	48%

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Mediators and Symptoms

- Each mediator could lead to specific clinical features. For instance:
  - **Histamine** is associated with headaches, hypotension, and pruritus
  - **Tryptase** with inflammation and fibrinogen lysis
- As a result, **mast-cell derived mediators** could contribute to the pathogenesis of not only allergic diseases, asthma and mastocytosis, but also to atopic dermatitis, psoriasis, myalgic encephalomyelitis/chronic fatigue syndrome, fibromyalgia, coronary artery disease, and obesity, as well as ASD
- Conditions associated with elevated serum or urine levels of any mast cell mediator, in the absence of any comorbidity that could otherwise explain such increases, should be considered **mast cell activation disorders**, or better yet be collectively termed '**Mast Cell Mediator Disorders** (MCMD).'

Theoharides TC, Tsilioni I, Ren H. **Recent advances in our understanding of mast cell activation - or should it be mast cell mediator disorders?**. *Expert Rev Clin Immunol*. 2019;15(6):639-656. doi:10.1080/1744666X.2019.1596800

Mediators and Symptoms

MEDIATOR	POSSIBLE EFFECTS
Histamine	Flushing, itching, diarrhea, hypotension
Leukotrienes	Shortness of breath
Prostaglandins	Flushing, bone pain, brain fog, cramping
Tryptase	Osteoporosis, skin lesions
Interleukins	Fatigue, weight loss, enlarged lymph nodes
Heparin	Osteoporosis, problems with clotting/bleeding
Tumor Necrosis Factor-α	Fatigue, headaches, body aches

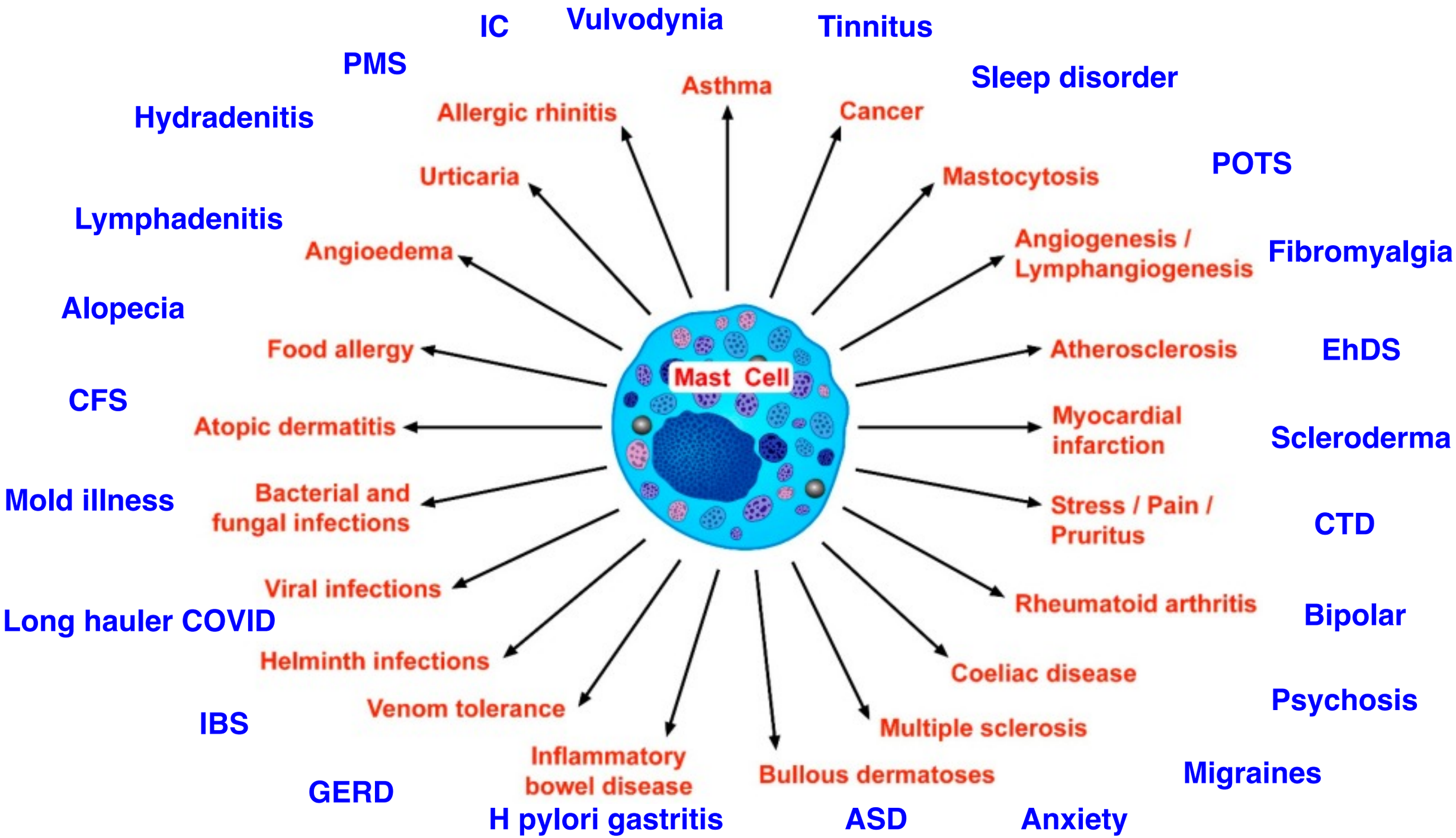
Source: The Mast Cell Disease Society - https://tmsforacure.org/symptoms/symptoms-and-triggers-of-mast-cell-activation/

Mast Cells and Diseases

- For several decades, mast cells and their mediators were essentially considered to play mainly a proinflammatory role in **allergic disorders**
- The spectrum of diseases in which mast cells and their mediators have been implicated has extended to include:
  - bacterial, fungal, viral, and helminth **infections**
  - several diseases of the **cardiovascular** and **gastrointestinal** systems and the joints
- **Wide spectrum of pathophysiological conditions in which mast cells and their mediators have been implicated**

Varricchi G, Marone G. **Mast Cells: Fascinating but Still Elusive after 140 Years from Their Discovery**. *Int J Mol Sci*. 2020;21(2):464. Published 2020 Jan 11. doi:10.3390/ijms21020464

Mast Cells and Diseases/Conditions



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Neurologic and Psychiatric Symptoms

- Neurologists and psychiatrists frequently encounter patients whose central and/or peripheral neurologic and/or psychiatric symptoms are accompanied by other symptoms
  - Investigation finds **no unifying cause**
  - Empiric therapy often provides **little to no benefit**
  - In studies over the last decade [2005-2015], at least **40–60%** of MCAD patients exhibited NPS
    - Prevalence of NPS in the general population is **below 10%**
  - The exact mechanisms that underlie NPS in MCAD are not yet understood in detail, but causal involvement of **acute or chronic excessive MC activation** seems certain

Afrin LB, Pöhlau D, Raithel M, Haenisch B, Dumoulin FL, Homann J, Mauer UM, Harzer S, Molderings GJ. **Mast cell activation disease: An underappreciated cause of neurologic and psychiatric symptoms and diseases**. *Brain Behav Immun*. 2015 Nov;50:314-321. doi: 10.1016/j.bbi.2015.07.002. Epub 2015 Jul 8. PMID: 26162709.

Neurologic and Psychiatric Symptoms

- Often labelled as psychosomatic complaints
- Many times misdiagnosed as Somatiform Disorder
- The highest densities of mast cells in brain: include the pituitary gland, hypothalamus, and thalamus
- Histamine is one of the most important neurotransmitters in the brain, activating H1 and H3

  —-> driving thermoregulation; regulation of food intake; cerebral seizures; arousal; anxiety, reward; and memory

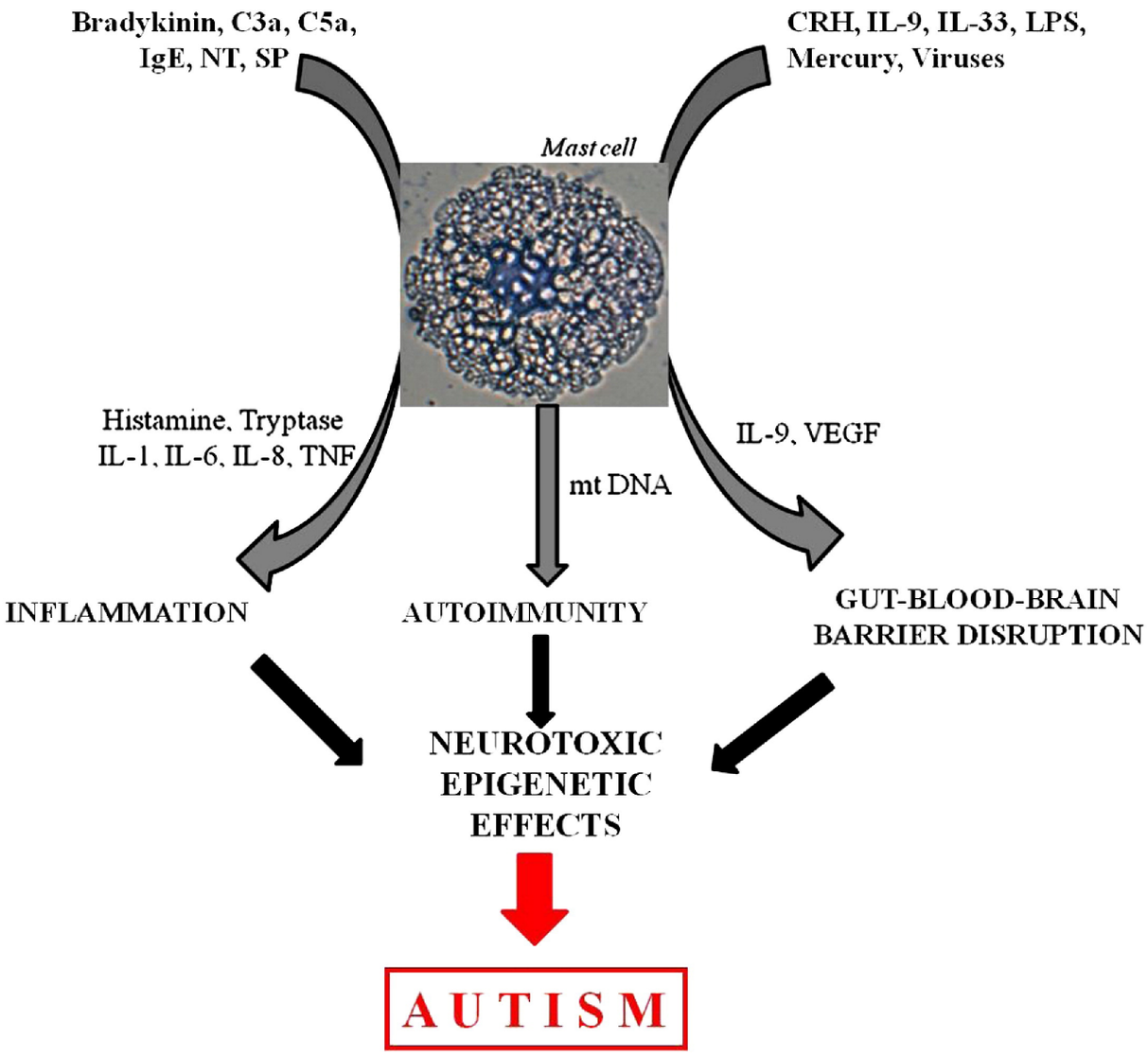
Afrin LB, Pöhlau D, Raithel M, Haenisch B, Dumoulin FL, Homann J, Mauer UM, Harzer S, Molderings GJ. **Mast cell activation disease: An underappreciated cause of neurologic and psychiatric symptoms and diseases**. *Brain Behav Immun*. 2015 Nov;50:314-321. doi: 10.1016/j.bbi.2015.07.002. Epub 2015 Jul 8. PMID: 26162709.

Mast Cells and Autism Spectrum Disorder

- Children with mastocytosis have a 10-fold higher risk of developing Autism Spectrum Disorder (ASD)
- **Allergic symptoms, due to mediators secreted from mast cells, have been significantly correlated with ASD severity**
- Large epidemiological studies have reported that allergies and asthma in preschoolers are significantly associated with ASD
- A similar conclusion was reached in a systematic review showing a significant **association between atopic dermatitis and ASD**
- The presence of allergic symptoms is strongly correlated with the presence of serum antibodies against brain peptides in children with ASD

Theoharides TC, Tsilioni I, Ren H. **Recent advances in our understanding of mast cell activation - or should it be mast cell mediator disorders?**. *Expert Rev Clin Immunol*. 2019;15(6):639-656. doi:10.1080/1744666X.2019.1596800

Mast Cells and Autism Spectrum Disorder

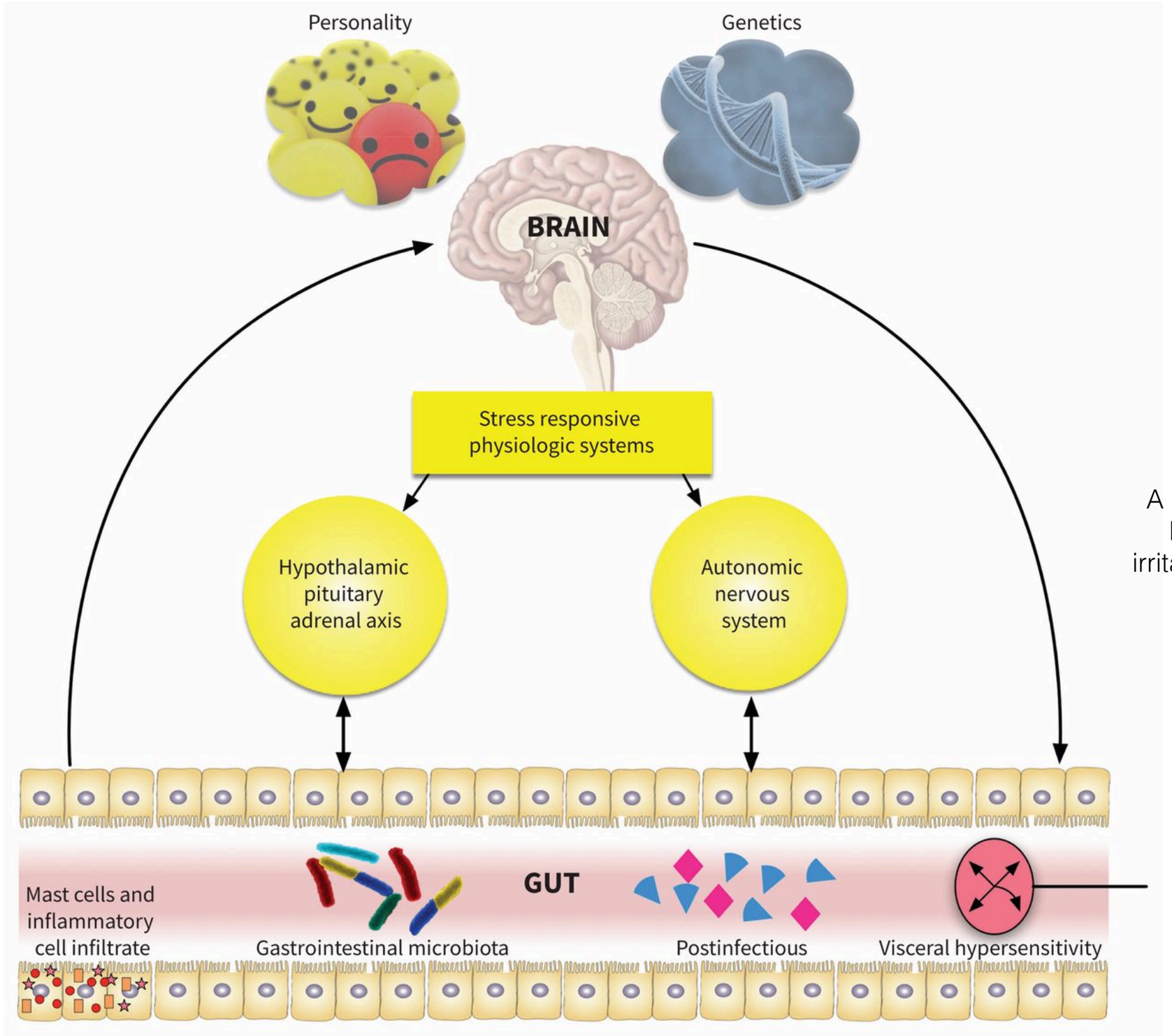


C3a=complement fragment 3a; CRH=corticotropin-releasing hormone;
IL=interleukin; LPS=lipopolysaccharide; mt=mitochondria; NT=neurotensin; SP=substance P;
TNF=tumor necrosis factor; VEGF=vascular endothelial growth factor

Fig. 3. Schematic representation of mast cell activation by allergic and non-immune triggers, and its possible involvement in the pathogenesis of autism.

Theoharides TC, Angelidou A, Alysandratos KD, Zhang B, Asadi S, Francis K, Toniato E, Kalogeromitros D. **Mast cell activation and autism**. *Biochim Biophys Acta.* 2012 Jan;1822(1):34-41. doi: 10.1016/j.bbadis.2010.12.017. Epub 2010 Dec 28. PMID: 21193035.

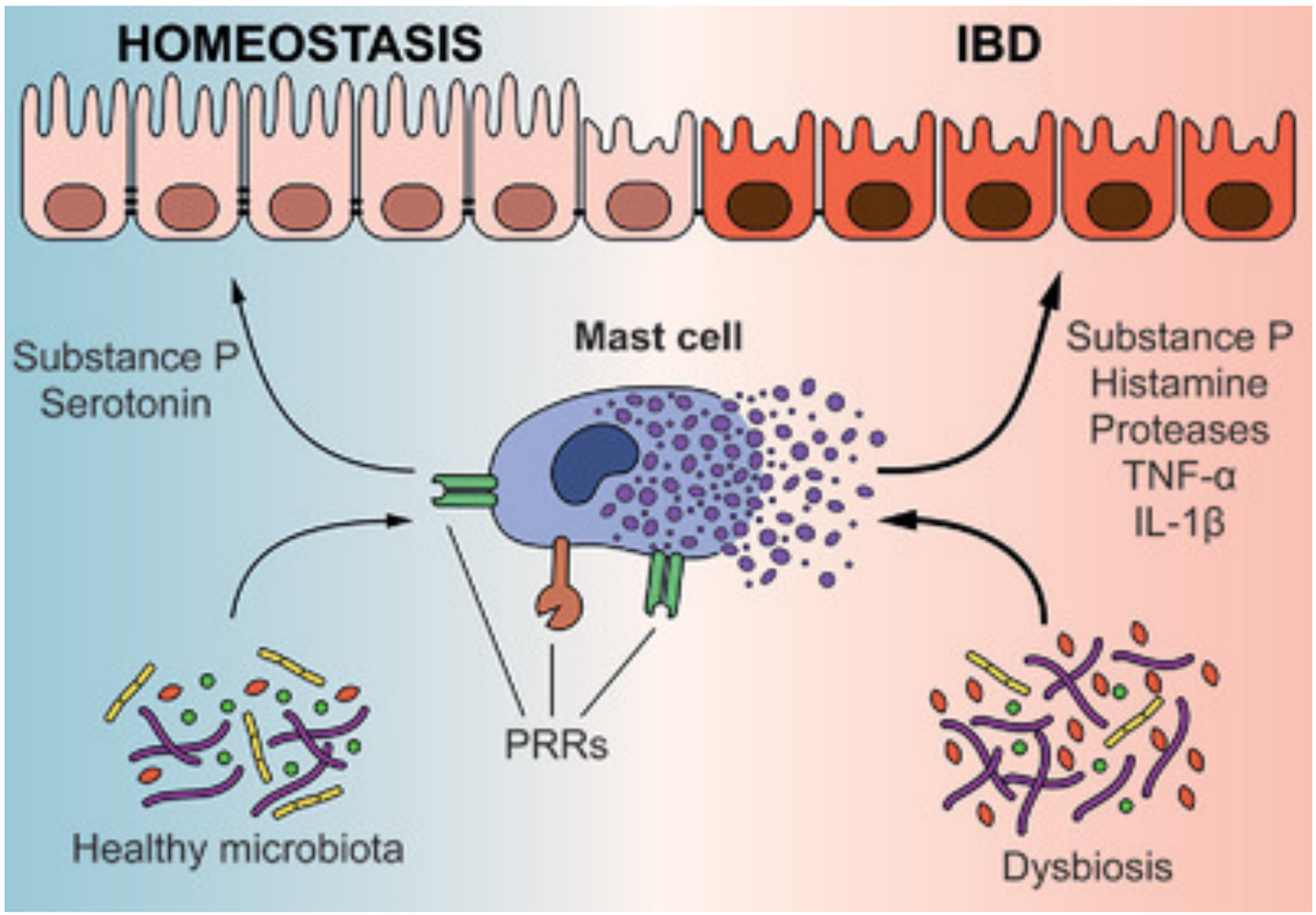
Mast Cells and IBS



A schematic summary of the factors that have been implicated in the pathophysiology of irritable bowel syndrome (IBS) within the context of the brain–gut axis.

Farmer AD, Wood E, Ruffle JK. **An approach to the care of patients with irritable bowel syndrome**. *CMAJ*. 2020 Mar 16;192(11):E275-E282. doi: 10.1503/cmaj.190716. PMID: 32179536; PMCID: PMC7083544.

Mast Cells and IBD



De Zuani, M., Dal Secco, C. and Frossi, B. (2018), **Mast cells at the crossroads of microbiota and IBD**. Eur. J. Immunol., 48: 1929-1937. https://doi.org/10.1002/eji.201847504

Mast Cells: Beyond Systemic Mastocytosis

Mast Cells: Beyond Systemic Mastocytosis

- Mast cell (MC) disease has long been thought to be just the rare disease of mastocytosis (in various forms, principally cutaneous and systemic), with aberrant MC mediator release at symptomatic levels due to **neoplastic** MC proliferation
- Recent discoveries show a new view of the realm of mast cell disease is in order, with mastocytosis capping a metaphorical iceberg now termed "**MC activation disease**" (MCAD, i.e. disease **principally** manifesting inappropriate MC activation)
- With the bulk of the iceberg being comprised of the recently recognized "MC activation syndrome" (MCAS), featuring **inappropriate MC activation to symptomatic levels with little to no inappropriate MC proliferation**

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MCAS and SM: Differences and Criteria

Proposed criteria defining Mast Cell Activation Syndrome (MCAS)	**WHO criteria defining Systemic Mastocytosis (SM)**
Major criteria	***Major criterion***
1. Multifocal or disseminated dense infiltrates of MCs in marrow and/or extracutaneous organ(s) (e.g., gastrointestinal or genitourinary tract)	Multifocal dense infiltrates of MCs (i.e., aggregates of >15 MCs) in marrow and/or other extracutaneous organ(s)
2. Constellation of clinical complaints attributable to pathologically increased MC activity (MC mediator release syndrome)	
Minor criteria	***Minor criteria***
1. Abnormal spindle-shaped morphology in >25% of MCs in marrow or other extracutaneous organ(s)	1. Abnormal spindle-shaped morphology in >25% of MCs in marrow or other extracutaneous organ(s)
2. Abnormal MC expression of CD2 and/or CD25 (i.e., co-expression of CD117/CD25 or CD117/CD2)	2. Abnormal marrow MC expression of CD2 and/or CD25 (i.e., co-expression of CD117/CD25 or CD117/CD2)
3. MC genetic changes (e.g., activating KIT codon 816 mutations) shown to increase MC activity	3. Activating KIT mutation at codon 816 in MCs in extracutaneous organ(s)
4. Evidence (typically from body fluids such as whole blood, serum, plasma, or urine) of above-normal levels of MC mediators including: Tryptase, Histamine or its metabolites (e.g., N-methylhistamine)	4. Serum total tryptase > 20 ng/ml (does not apply in patients who have associated hematologic non-mast-cell lineage disease)
5. Symptomatic response to inhibitors of MC activation or MC mediator production or action	

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MCAS and SM: Differences and Criteria

- The diagnosis **MCAS** is made upon fulfillment of either:
  - both major criteria
  - or the second criterion plus at least one minor criterion
- According to the WHO criteria, the diagnosis **SM** is established if
  - the major criterion and at least one minor criterion or at least three minor criteria are fulfilled

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Mast Cells: MCAD / MCAS

MCAD/MCAS: Diagnosis

Due to MCs'

- wide distribution,
- enormous range in normal biological activities, and
- great heterogeneity in mediator expression patterns

the norm: diagnostically challenging, extreme heterogeneity in clinical presentation of MCAD

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MCAD/MCAS: Diagnosis

- MCAD (especially MCAS) is reasonable to suspect in **poorly explained chronic multisystem polymorbidity (particularly if inflammatory)**
- MCAD patients often acquire many idiopathic diagnoses
- MCAD both **may be comorbid with definitively diagnosed illness and can cause such illness**
- Usually recognised in retrospect, symptoms manifest typically initially during **adolescence or even earlier**
- **Symptoms can occur in any organs/tissues/systems, often temporarily staggered** (i.e. different symptoms at different times), fluctuating over years to decades
- Escalation of symptoms above baseline soon occurs **following major stressors**, either physiologic (e.g puberty, menopause) or pathologic (physical or psychological trauma)

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MCAD/MCAS: Diagnosis

- Classic flushing and anaphylaxis often spur consideration of MCAD, especially SM, but **less distinctive symptoms often are the only signs**, explaining typically great latency in diagnosis of SM and MCAS
- **Symptoms course chronically or episodically**, waxing and waning with varying frequencies and amplitudes
- **Aberrant reactivities** — dietary, medication, and/or environmental — may be numerous
- Medication reactivities often are directed against **excipients** (i.e. colouring agents, preservatives, and fillers)

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Diagnostic Approach to MCAD

Establish Suspicion:

Signs of mastocytosis (e.g., urticaria pigmentosa, unprovoked flushing or anaphylaxis, wasting, end-organ dysfunction, etc.)

Multisystem symptoms of MC activation (Table 1; consider use of validated questionnaire)

More symptoms/findings than can be explained by definitively established diagnoses; odd/strange symptoms/findings; relevant differential diagnoses excluded (Supplementary Table 5)

Poor response to treatment of definitively established diagnoses

↓

Initial Testing:

Biopsy of lesions of suspected cutaneous mastocytosis

Serum tryptase persistently > 20 ng/ml (or, per [49], increase of 20% + 2 ng/ml during or within 4 hours after a symptomatic period):

- bilateral marrow aspiration/biopsy including MC-specific immunohistochemical staining (e.g., CD117, tryptase, toluidine blue, Giemsa, Alcian blue), multicolor flow cytometry for co-expression of CD117/CD25, CD117/CD2, and molecular testing for KIT mutations as available (PCR for KIT^{D816V} at a minimum)
- biopsy of other extracutaneous tissues (e.g., GI tract) as appropriate, for MC-specific testing as above (Supplementary Figure 2)

Complete blood count with manual differential
Common serum chemistries
Quantitative immunoglobulin profile if frequent infections and/or delayed healing
Coagulation evaluation if easy bruising or bleeding or thromboembolic events

↓

Additional MC Mediator Testing:

Serum chromogranin A (avoid proton pump inhibitors for ≥ 5 days before testing)
Chilled plasma for prostaglandin (PG) D_2 (and/or 11-β-$PGF_{2\alpha}$) (avoid non-steroidal anti-inflammatory drugs for ≥ 5 days before testing)
Chilled plasma histamine
Chilled plasma heparin (if not on exogenous heparin products)
Chilled random and 24-hour urine collections for PGD_2 (and/or 11-β-$PGF_{2\alpha}$) and *N*-methylhistamine
Chilled urine for leukotriene E4 (if necessary)

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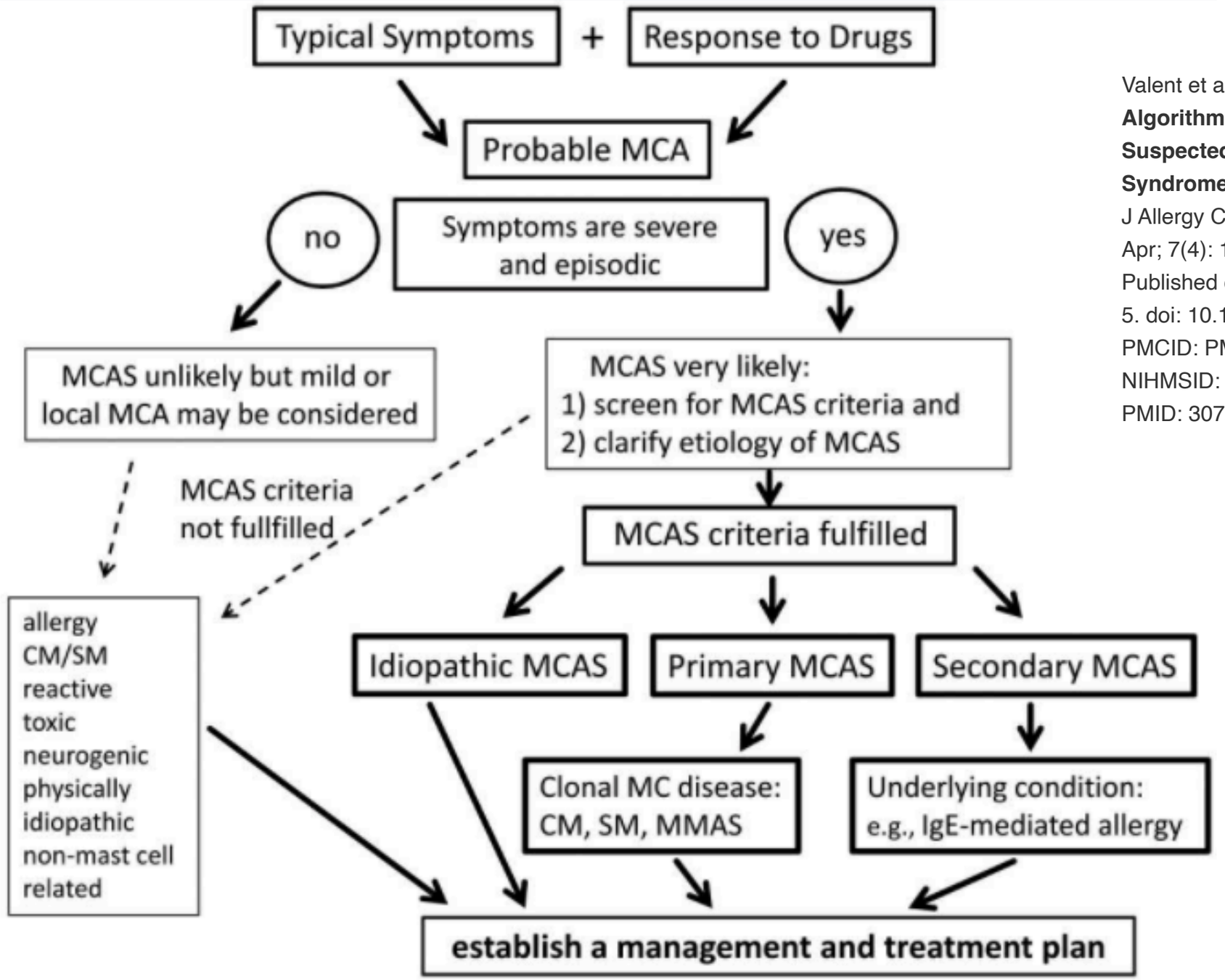
Diagnostic Approach to MCAD



Valent et al **Proposed Diagnostic Algorithm for Patients with Suspected Mast Cell Activation Syndrome (MCAS)**
J Allergy Clin Immunol Pract. 2019 Apr; 7(4): 1125–1133.e1.
Published online 2019 Feb 5. doi: 10.1016/j.jaip.2019.01.006
PMCID: PMC6643056
NIHMSID: NIHMS1518625
PMID: 30737190

Mast Cell Instability

Mast Cell Instability

- There is a **spectrum** of mast cell instability
- MCAD may **not be so not black and white**
- Mast cell disorders don’t always fit neatly into a name-the-disease box
- **Wide variability** in presentation, symptoms, severity, triggers, and treatment response
- Lack of definitive diagnostic criteria

Mast Cell Instability

- As functional/integrative medicine practitioners, we operate in grey areas
- We recognize the concepts of **“continuum” - “individual variability” - “susceptibility”**
- These grey area conditions warrant greater investigation, understanding, and **personalization** of treatment
- We have the opportunity to provide the more effective care to patients who have been searching - perhaps underserved, misdiagnosed, undiagnosed, or dismissed

Mast Cell Instability

- The best way to describe the status of the mast cells is that they are **‘unstable’**, exhibiting aberrant stimulation

- The ‘unstable’ status of mast cells may be **affected by positive and negative signals**, lower stimulation threshold, **or even ‘normal’ secretion of mast cell mediators, but with an abnormal response of the surrounding tissues** (e.g. deficiency of catabolic enzymes such as DAO and HNMT)

- Unstable mast cells may retain a ‘metabolic memory’ of past triggers that **prime** mast cells to respond more rapidly and more severely to exposure of the same or different triggers even though the **original trigger may no longer be present**

Theoharides TC, Tsilioni I, Ren H. **Recent advances in our understanding of mast cell activation - or should it be mast cell mediator disorders?**. *Expert Rev Clin Immunol*. 2019;15(6):639-656. doi:10.1080/1744666X.2019.1596800

Mast Cell Instability: Management

Mast Cell Instability: Management

- Modulation of MC hyperactivity
- Reduction of the release of inflammatory factors
- Goal: prevent
    - the chronicity of inflammation,
    - the evolution of pain,
    - and also the worsening of the associated depression and anxiety

    — “may constitute a new frontier of pharmacological intervention”

Traina G. **Mast Cells in Gut and Brain and Their Potential Role as an Emerging Therapeutic Target for Neural Diseases**. Front Cell Neurosci. 2019 Jul 30;13:345. doi: 10.3389/fncel.2019.00345. PMID: 31417365; PMCID: PMC6682652.

Mast Cell Instability: Management

- As the primary feature of MCAD is inappropriate mast cell activation, treatment invariably involves:
  - **Trigger identification/avoidance**
  - **Control of mast cell mediator production/action**
- The tolerability and efficacy of most MCAD therapies become evident within 1-2 months
- Successful regimens appear **highly personalized**, possibly reflecting mutational heterogeneity
- In most MCAD patients, some improvement is usually attainable, although patient and providers must exercise patience; sometimes many lines (and formulations) of therapy must be tried

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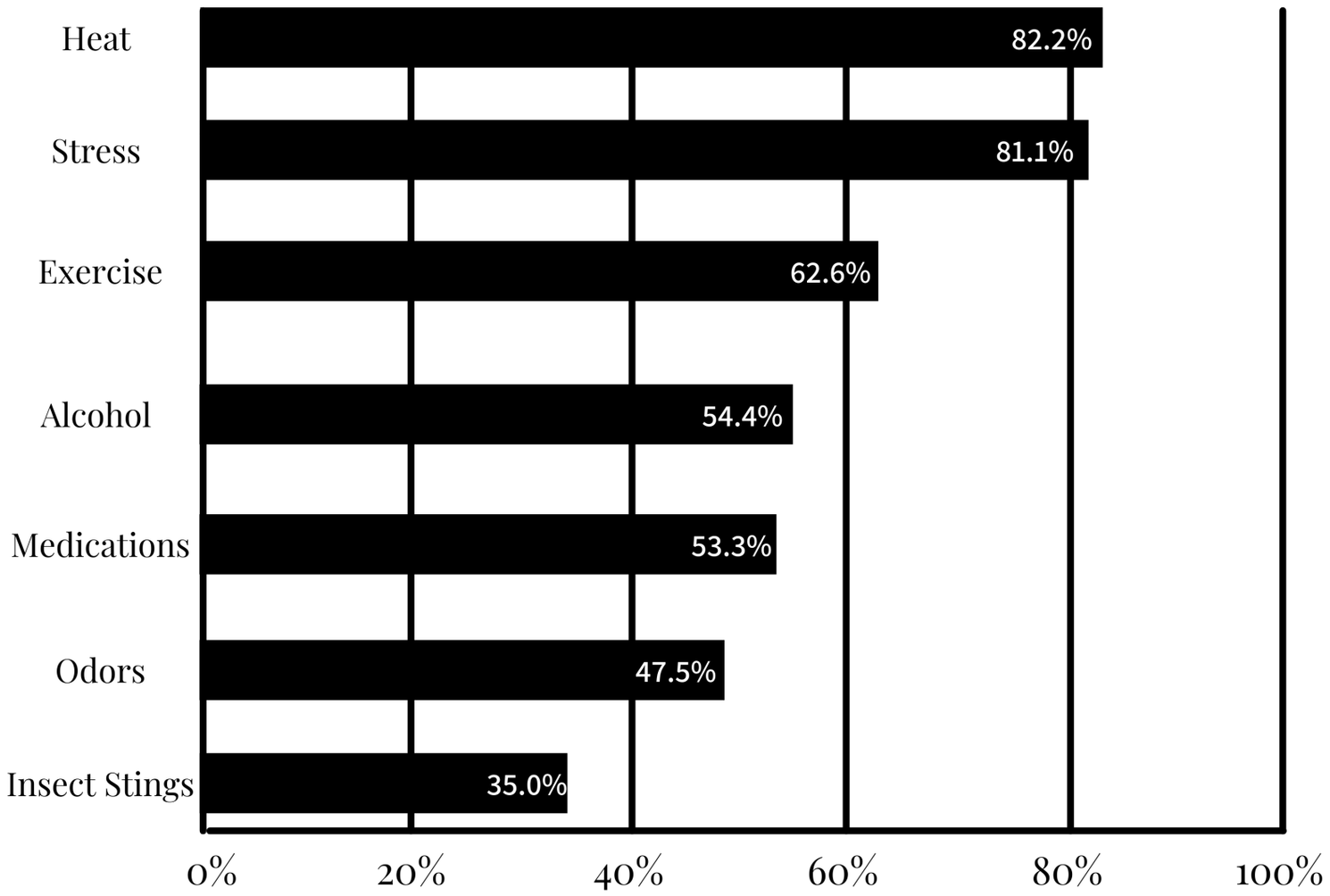
Common Mast Cell Triggers

- Alcohol
- Estrogen
- Heat; sudden temperature increases
- Histamine-rich foods
- Histamine-releasing foods
- Hymenoptera stings
- Mechanical irritation; physical stimuli (pressure, friction)
- Medications and supplements: ACE inhibitors, antibiotics, beta blockers, niacin, NSAIDs, opioids
- Metals
- Mold and mycotoxins
- Preservatives in food
- Stressful conditions
- Ultraviolet radiation
- Viruses

Theoharides TC, Tsilioni I, Ren H. **Recent advances in our understanding of mast cell activation - or should it be mast cell mediator disorders?**. *Expert Clin Immunol*. 2019;15(6):639-656. doi:10.1080/1744666X.2019.1596800

Lawrence B. Afrin, Joseph H. Butterfield, Martin Raithel & Gerhard J. Molderings (2016) **Often seen, rarely recognized: mast cell activation disease – a guide to diagnosis and therapeutic options**, Annals of Medicine, 48:3, 190-201, DOI: 10.3109/07853890.2016.1161231

Common Mast Cell Triggers



Most commonly reported symptom triggers among patients with MCAD (including MCAS and SM)

Jennings S, Russell N, Jennings B, Slee V, Sterling L, Castells M, Valent P, Akin C. **The Mastocytosis Society survey on mast cell disorders: patient experiences and perceptions**. J Allergy Clin Immunol Pract. 2014 Jan-Feb;2(1):70-6. doi: 10.1016/j.jaip.2013.09.004. Epub 2013 Dec 3. PMID: 24565772.

Management: First Line Therapies for MCAD

- **H1 antihistamines**
  - *Block mutual activation of mast cells via H1-histamine receptors; antagonize H1-histamine receptor-mediated symptoms*
- **H2 antihistamines**
  - *Block mutual activation of mast cells via H2-histamine receptors; antagonize H2-histamine receptor-mediated symptoms*
- **Cromoglicic acid (cromolyn)**
  - *GPR35; modulation of chloride current*
- **Vitamin C**
  - *Increased degradation of histamine; decrease of histamine formation by inhibition of histidine decarboxylase*

Molderings GJ, Haenisch B, Brettner S, et al. **Pharmacological treatment options for mast cell activation disease**. *Naunyn Schmiedebergs Arch Pharmacol*. 2016;389(7):671-694. doi:10.1007/s00210-016-1247-1

Natural Mast Cell Stabilizers

- Vitamin C (slow release 500-1000 mg qd)
- Quercetin (250-1000 mg bid)
- Luteolin (100-400 mg bid)
- Chondroitin sulphate
- EGCG
- Silymarin
- Resveratrol
- Curcumin
- Theanine
- N-acetylcysteine (300-600 mg bid; some may react/anaphylax)
- Melatonin

Finn DF, Walsh JJ. **Twenty-first century mast cell stabilizers**. *Br J Pharmacol*. 2013;170(1):23-37. doi:10.1111/bph.12138

Lawrence B. Afrin, Joseph H. Butterfield, Martin Raithel & Gerhard J. Molderings (2016) **Often seen, rarely recognized: mast cell activation disease – a guide to diagnosis and therapeutic options**, Annals of Medicine, 48:3, 190-201, DOI: 10.3109/07853890.2016.1161231

Pham L, Baiocchi L, Kennedy L, Sato K, Meadows V, Meng F, Huang CK, Kundu D, Zhou T, Chen L, Alpini G, Francis H. **The interplay between mast cells, pineal gland, and circadian rhythm: Links between histamine, melatonin, and inflammatory mediators**. J Pineal Res. 2021 Mar;70(2):e12699. doi: 10.1111/jpi.12699. Epub 2020 Nov 29. PMID: 33020940.

Mast Cell Instability: Management

- Avoidance of common food triggers and allergens: **gluten, dairy, yeast**, spices, alcohol, histamine-rich and histamine-releasing foods
- Avoidance of triggering **medications** (ACE inhibitors, beta blockers, NSAIDs)
- Gut **microbiome** support
- Stabilization with **vitamin C**, quercetin, other natural mast cell stabilizers
- Optimize **vitamin D**
- Restoration of circadian rhythm in MCs with **melatonin**
- Investigation and management of **histamine intolerance**
- Investigation and avoidance of additional environmental triggers: **mold, metals; detoxification**
- Support of **estrogen/**progesterone balance

Management: Diet

- Temporary **abstinence from gluten-, yeast-, and cow's milk protein**-containing foods during the initial month of drug therapy can improve response rate
  - Possibly more from reducing trigger exposure than truly improving medication efficacy.
- Avoid common food triggers: high histamine foods [fermented foods, aged foods, processed foods, leftovers - **food should be as fresh as possible**], histamine-releasing foods [tomatoes, citrus fruits, chocolate, dyes, additives]
- Avoid alcohol

Lawrence B. Afrin, Joseph H. Butterfield, Martin Raithel & Gerhard J. Molderings (2016) **Often seen, rarely recognized: mast cell activation disease – a guide to diagnosis and therapeutic options**, Annals of Medicine, 48:3, 190-201, DOI: 10.3109/07853890.2016.1161231

Management: Triggering Medications

ACE inhibitors

Antibiotics

Beta blockers

NSAIDs

Neuromuscular junction blocking agent

Opioids

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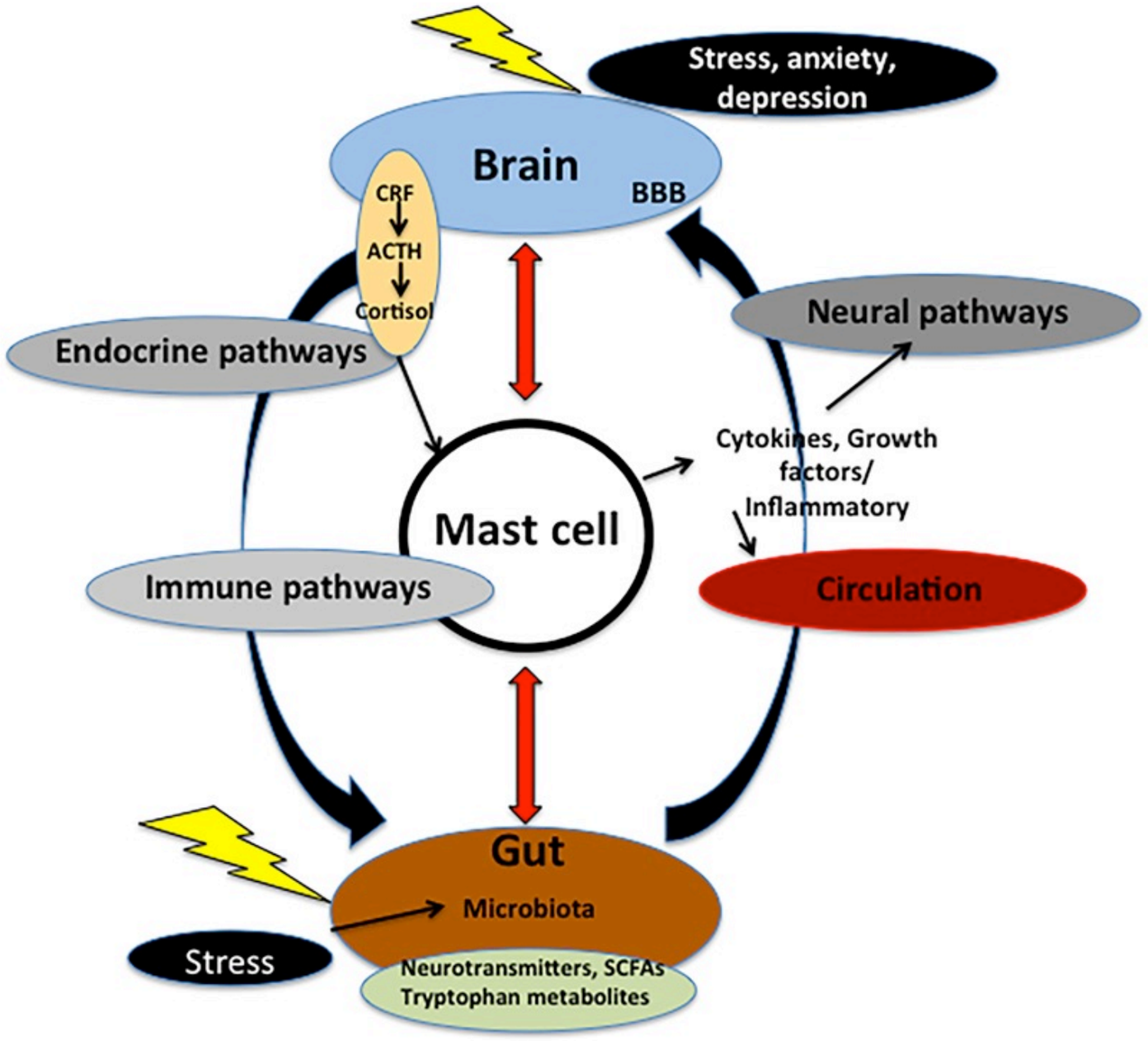
Clin Immunol. 2019;15(6):639-656. doi:10.1080/1744666X.2019.1596800

Management: Gut Microbiome



Traina G. **Mast Cells in Gut and Brain and Their Potential Role as an Emerging Therapeutic Target for Neural Diseases**. Front Cell Neurosci. 2019 Jul 30;13:345. doi: 10.3389/fncel.2019.00345. PMID: 31417365; PMCID: PMC6682652.

Management: Gut Microbiome

- The MC is particularly responsive to microbiota conditions and its stabilization through appropriate combinations of probiotics could represent a new potential therapeutic tool
- **The goal is to stabilize the MC, and do it starting from the intestine**

Traina G. **Mast Cells in Gut and Brain and Their Potential Role as an Emerging Therapeutic Target for Neural Diseases**. Front Cell Neurosci. 2019 Jul 30;13:345. doi: 10.3389/fncel.2019.00345. PMID: 31417365; PMCID: PMC6682652.

Management: Gut Microbiome

- Altered occurrence of Proteobacteria and Bifidobacteriaceae, reduced alpha-diversity as well as elevated stool zonulin levels suggest dysbiosis and intestinal barrier dysfunction in histamine intolerant patients, **which may in turn play an important role in driving disease pathogenesis**
- **Microorganisms, such as bacteria and fungi, can induce MC activation**
- Mycoplasma pneumoniae and Streptococcus pneumoniae **induce MC degranulation**
- Other microorganisms; **probiotics are able to reduce their activation**
- Impacts of any given bacterium likely are not 1-sided
  - In mice, Escherichia coli attenuates serotonin and β-hexosaminidase secretion but induces histamine release

Traina G. **Mast Cells in Gut and Brain and Their Potential Role as an Emerging Therapeutic Target for Neural Diseases**. Front Cell Neurosci. 2019 Jul 30;13:345. doi: 10.3389/fncel.2019.00345. PMID: 31417365; PMCID: PMC6682652.

Afrin LB, Khoruts A. **Mast Cell Activation Disease and Microbiotic Interactions**. Clin Ther. 2015 May 1;37(5):941-53. doi: 10.1016/j.clinthera.2015.02.008. Epub 2015 Mar 12. PMID: 25773459.

Schink M, Konturek PC, Tietz E, Dieterich W, Pinzer TC, Wirtz S, Neurath MF, Zopf Y. **Microbial patterns in patients with histamine intolerance**. J Physiol Pharmacol. 2018 Aug;69(4). doi: 10.26402/jpp.2018.4.09. Epub 2018 Dec 9. PMID: 30552302.

Management: Beneficial Microbes

- Some probiotic strains are able to stabilize MCs, especially ***L. rhamnosus*** *GG*
- Treatment with ***Bifidobacterium longum*** KACC 91563 can control the number of MCs in the gut lamina propria
- Beneficial effects of a combination of ***Bacillus subtilis*** **and** ***Enterococcus faecium*** **(LCBE)** could inhibit the degranulation of MCs
  - Levels of histamine were also decreased after administration of **LCBE**
- Probiotics influence mucosal MCs but also could affect MCs in the brain through microbiota-gut-brain axis
  - ***Lactobacillus reuteri*** and **Bifidobacteria**
- **Saccharomyces boulardii** associated with a significant increase in DAO activity

Traina G. **Mast Cells in Gut and Brain and Their Potential Role as an Emerging Therapeutic Target for Neural Diseases**. Front Cell Neurosci. 2019 Jul 30;13:345. doi: 10.3389/fncel.2019.00345. PMID: 31417365; PMCID: PMC6682652.

Moré MI, Vandenplas Y. **Saccharomyces boulardii CNCM I-745 Improves Intestinal Enzyme Function: A Trophic Effects Review**. Clin Med Insights Gastroenterol. 2018 Feb 9;11:1179552217752679. doi: 10.1177/1179552217752679. PMID: 29449779; PMCID: PMC5808955.

Management: Microbiome By-products

- Analogous to focussing on **the mediators** which are secondary to mast cell activity, can **the by-products** of gut flora be leveraged for mast cell stability?
- SCFA's and butyrate in particular:
  - **Sodium butyrate reduced the percentage of degranulated MCs** and their inflammatory mediator content
  - Sodium butyrate reduces the expression of MC-specific tryptase, TNF-α, and IL-6

Traina G. **Mast Cells in Gut and Brain and Their Potential Role as an Emerging Therapeutic Target for Neural Diseases**. Front Cell Neurosci. 2019 Jul 30;13:345. doi: 10.3389/fncel.2019.00345. PMID: 31417365; PMCID: PMC6682652.

GI-MAP
GI Microbial Assay Plus

OPPORTUNISTIC/OVERGROWTH MICROBES

DYSBIOTIC & OVERGROWTH BACTERIA	Result	Reference
Bacillus spp.	2.56e5	< 1.76e6
Enterococcus faecalis	1.81e3	< 1.00e4
Enterococcus faecium	< dl	< 1.00e4
Morganella spp.	< dl	< 1.00e3
Pseudomonas spp.	< dl	< 1.00e4
Pseudomonas aeruginosa	< dl	< 5.00e2
Staphylococcus spp.	< dl	< 1.00e4
Staphylococcus aureus	3.83e2	< 5.00e2
Streptococcus spp.	< dl	< 1.00e3
COMMENSAL OVERGROWTH MICROBES		
Desulfovibrio spp.	1.84e3	< 7.98e8
Methanobacteriaceae (family)	1.24e8	< 3.38e8
INFLAMMATORY & AUTOIMMUNE-RELATED BACTERIA		
Citrobacter spp.	< dl	< 5.00e6
Citrobacter freundii	< dl	< 5.00e5
Klebsiella spp.	< dl	< 5.00e3
Klebsiella pneumoniae	< dl	< 5.00e4
M. avium subsp. paratuberculosis	< dl	< 5.00e3
Proteus spp.	< dl	< 5.00e4
Proteus mirabilis	< dl	< 1.00e3
COMMENSAL INFLAMMATORY & AUTOIMMUNE RELATED BACTERIA		

Patient: Ima Sample Accession: 00000000-0001

GI Microbial Assay Plus

HELICOBACTER PYLORI

H. PYLORI & VIRULENCE FACTORS	Result		Reference
Helicobacter pylori	**2.90e3**	**High ↑**	< 1.00e3
Virulence Factor, babA	**Positive**		Negative
Virulence Factor, cagA	**Positive**		Negative
Virulence Factor, dupA	Negative		Negative
Virulence Factor, iceA	Negative		Negative
Virulence Factor, oipA	Negative		Negative
Virulence Factor, vacA	Negative		Negative
Virulence Factor, virB	**Positive**		Negative
Virulence Factor, virD	**Positive**		Negative

COMMENSAL/KEYSTONE BACTERIA

COMMENSAL BACTERIA	Result	Reference
Bacteroides fragilis	8.98e10	1.6e9 - 2.5e11
Bifidobacterium spp.	1.89e10	> 6.7e7
Enterococcus spp.	2.45e7	1.9e5 - 2.0e8
Escherichia spp.	2.14e8	3.7e6 - 3.8e9
Lactobacillus spp.	6.55e6	8.6e5 - 6.2e8
Enterobacter spp.	2.07e6	1.0e6 - 5.0e7

INTESTINAL HEALTH MARKERS

DIGESTION	Result	Reference
Steatocrit	<dl	< 15 %
Elastase-1	>750	> 200 ug/g
GI MARKERS		
β-Glucuronidase	2584 H	< 2486 U/mL
Occult Blood - FIT	0	< 10 ug/g
IMMUNE RESPONSE		
Secretory IgA	552	510 - 2010 ug/g
Anti-gliadin IgA	157	< 175 U/L
Eosinophil Activation Protein (EDN, EPX)	1.40	< 2.34 ug/g
INFLAMMATION		
Calprotectin	116	< 173 ug/g
ADD-ON TESTS		
Zonulin	177.0 H	< 175 ng/g

Management: Vitamin C

- Vitamin C as a **first-line therapy** for MCAD:
  - Increased degradation of histamine
  - Decrease of histamine formation by inhibition of histidine decarboxylase

- Vitamin C has beneficial effects on systemic mast cell related inflammation
  - Deficiency is associated with impaired cell-mediated immunity

- Vitamin C may improve this interaction and be **used as an adjuvant therapeutic compound in several inflammatory and allergic diseases**

Molderings GJ, Haenisch B, Brettner S, et al. **Pharmacological treatment options for mast cell activation disease**. *Naunyn Schmiedebergs Arch Pharmacol*. 2016;389(7):671-694. doi:10.1007/s00210-016-1247-1

BD, Y. S. (2016). **Relationship between Vitamin C, mast cells and inflammation**. Journal of Nutrition & Food Sciences, 06(01). doi:10.4172/2155-9600.1000456

Management: Vitamin D

- Known to play an immunoregulatory role re: MCs
- In fact, vitamin D is required to maintain stability of MCs (Liu et al., 2017)
- A **deficiency of vitamin D results in MC activation**
  - MCs express 25-hydroxyvitamin D- 1α-hydroxylase
    - enables them to convert inactive 25-hydroxyvitamin D3 (25OHD3) to biologically active 1α,25(OH)2D3 (Yip et al., 2014)
  - 1α,25(OH)2D3 favors apoptosis and inhibits maturation of bone marrow-derived MC

Traina G. **Mast Cells in Gut and Brain and Their Potential Role as an Emerging Therapeutic Target for Neural Diseases**. Front Cell Neurosci. 2019 Jul 30;13:345. doi: 10.3389/fncel.2019.00345. PMID: 31417365; PMCID: PMC6682652.

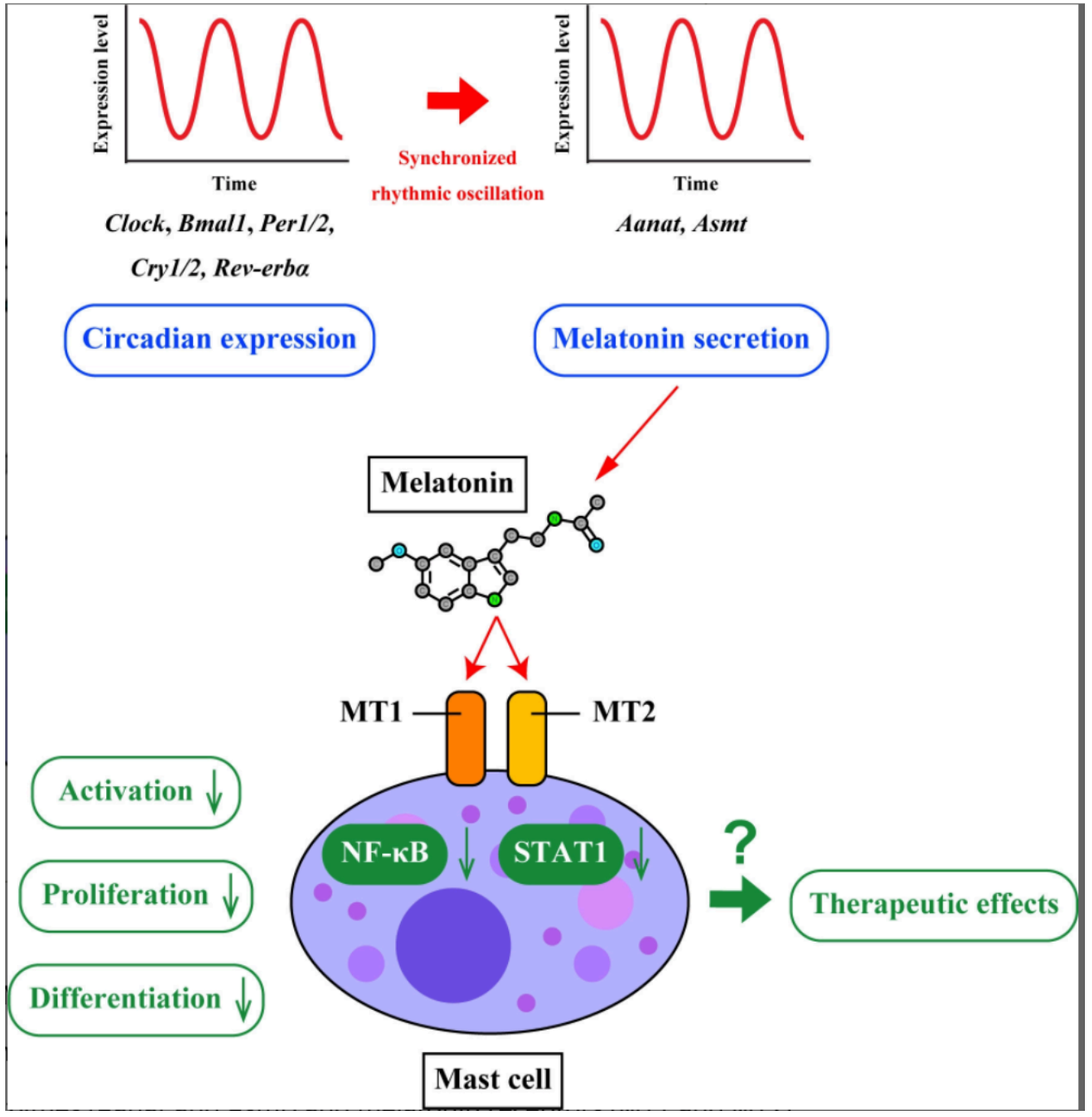
CODES	TEST DESCRIPTION	RESULTS	REFERENCE RANGE		OUTSIDE NORMAL LIMITS
	This report is intended only for the use of the addressee and contains confidential information. Any dissemination of this information is prohibited. If you have received this report in error please notify the sender at (905)790-3030 or 1-800-565-5721 and forward all documentation to Customer Service, 115 MIDAIR COURT, BRAMPTON, Ontario, L6T 5M3				
	C H E M I S T R Y				
25	HYDROXY VITAMIN D	29.	DEFICIENCY:	< 25 nmol/L	29.
			INSUFFICIENCY:	25 - 75 nmol/L	
			SUFFICIENCY:	76 - 250 nmol/L	
			TOXICITY:	> 250 nmol/L	

Management: Melatonin

- **MC quantity and activity are controlled by daily rhythmic variation**, a circadian clock under the regulation of a specific set of clock genes
- Daily expressions of melatonin-forming enzymes and melatonin receptors (MT1 and MT2) are in synchronized rhythmic oscillation with expression of clock genes
- Melatonin is also a key mediator which recognizes potential damage and risk status in MCs via NF-κB and STAT1 pathways.
- **Binding of melatonin to MT1 and MT2 leads to the inhibition of NF-κB activation, which in turn down-regulates MC activation, proliferation, and differentiation.**
- Restoring circadian rhythms in MCs by targeting melatonin and histamine may be promising therapeutic strategy for MC-mediated inflammatory diseases

Pham, L, Baiocchi, L, Kennedy, L, et al. **The interplay between mast cells, pineal gland, and circadian rhythm: Links between histamine, melatonin, inflammatory mediators**. *J Pineal Res*. 2021; 70:e12699. https://doi.org/10.1111/jpi.12699

Management: Melatonin



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YOUR HEALTH

YOUR CHOICE

YOUR HEALTH

YOUR CHOICE

Histamine Metabolism and Intolerance

Histamine Metabolism and Intolerance

Histamine sensitivity: one must also consider patients who are either sensitive to histamine or have **mutations in the gene diamine oxidase [DAO]** rendering them unable to metabolize histamine.

Theoharides TC, Tsilioni I, Ren H. **Recent advances in our understanding of mast cell activation - or should it be mast cell mediator disorders?**. *Expert Rev Clin Immunol*. 2019;15(6):639-656. doi:10.1080/1744666X.2019.1596800

Histamine Metabolism and Intolerance

- Variants in DAO or HNMT genes; decreased DAO/HNMT activity may lead to poor metabolism of endogenous and exogenous histamine, exacerbating the effects of histamine-mediated mast cell activation

- Investigate and support levels of DAO co-factors: vitamin B6, zinc, copper, vitamin C

- Avoid DAO blockers: some antihistamines/H2 blockers i.e. Cimetidine, NAC, alcohol, green and black tea

- Avoid high histamine and histamine releasing foods (esp. fermented foods, processed or refined foods, aged foods)

- Support methylation

Histamine Metabolism and Intolerance

HISTAMINE ACCUMULATION

Food Sources

- Histamine containing foods
- Fermented or aged foods; leftovers
- Alcohol
- Food additives, artificial flavours & colours e.g. glutamates, nitrates, sulfites, benzoates
- Lectins

Endogenous Histamine

- Histamine-producing gut bacteria
- Excess or dysregulated estrogen
- Mast cell activation
- Food sensitivities e.g. gluten
- Melatonin deficiency

Mast Cell Stimulation

- Medications (antibiotics, NSAIDs, antihistamines, more)
- Allergies
- Chemical exposure
- Extreme temperatures
- Chronic stress
- Strenuous exercise
- Insect bites
- Infections

HISTAMINE DEGRADATION

- Mutation of Diamine Oxidase (DAO) gene
- Mutation of Histamine N-Methyltransferase (HNMT) gene
- Gastrointestinal disorders (IBD, IBS, Ulcerative Colitis, Crohn's, dysbiosis, Celiac Disease)
- Food / Beverages that Block DAO
- Medications that Block DAO
- Vitamin & mineral deficiencies including magnesium, B12

Histamine in functional gastrointestinal disorders

- In westernized countries, adverse reactions to ingested foods are reported to affect up to **20% of the population**

- Functional, nonspecific, non-allergic gastrointestinal complaints are mainly due to the **intolerance/malabsorption** of carbohydrates (lactose and fructose), proteins (gluten), and biogenic amines (histamine)

- Histamine and, histamine intolerance, should be considered in differential diagnoses of patients with **functional, nonspecific, non-allergic gastrointestinal complaints**

Wolfgang J. Schnedl & Dietmar Enko (2021) Considering histamine in functional gastrointestinal disorders, Critical Reviews in Food Science and Nutrition, 61:17, 2960-2967, DOI: 10.1080/10408398.2020.1791049

Health Care Professional: John Gannage
Address: 300 Main St N, Markham, Ontario L3P 1Y8

Sample collection: 2022-11-15

ZONULIN FAMILY PEPTIDES (ZONULIN FP) + HISTAMINE : DIAMINE OXIDASE (DAO)

Zonulin FP Result **11.1 ng/ml** **Elevated**

Histamine Result **1.34 ng/ml**

DAO Result **9.07 ng/ml**

Histamine : DAO Ratio (x1000) **148**

John Gannage
Test date: 10/06/2019


Diet


Sensitivities


Specific Nutrient Needs

Physical Fitness


Mental Wellness


Detox


Obesity Risk


Hormonal Health

My Genes. My Health.

We are delighted that you have chosen to purchase our LoveMyHealth Lifestyle Genetic Test so that you can begin to live the best life you can! In your personalized report, you will find very helpful and comprehensive information about you. We designed our report with you in mind; easy to use and understand, and actionable. The DNA Labs team is excited to present your unique results to you. Just click, explore, and learn how your very own "Owners Manual", your DNA, can reveal so much valuable information about you!

Using cutting edge genetic technology, we have analyzed your DNA, looking at 84 unique variants across 65 genes that collectively dictate how your “owners manual” helps to shape your personalized action plan. Based on this information, we have created actionable nutritional, exercise, and lifestyle recommendations for you related to dietary and nutrient needs, food sensitivities, fitness planning and physical health management, as well as cardiovascular and metabolic health. Each section of the report provides you with direct changes that you can make today and empowers you to improve your health and well-being!

Thanks for purchasing our Love My Health genetic test; we hope that you use the actionable information within your report to begin to live life great!

Histamine Removal

Allergic responses are the result of your body's immune system reacting to harmless substances. During an allergic response, specific cells in your body produce and release histamines, molecules that are part of your body's natural defense system and are ultimately responsible for producing common allergy symptoms including itching, sneezing, inflammation, and anaphylaxis. Usually, two enzymes within your body, DAO and HNMT, metabolize histamines quickly, alleviating you of your annoying allergy symptoms. However, specific genetic variants cause underproduction of these enzymes, resulting in excess histamine within your body and ultimately, histamine intolerance, which is characterized by consistent allergic symptoms. Certain foods contain high levels of histamines, and avoidance of these foods can help with the treatment of histamine intolerance. Read on to learn what your genes say about how your body processes histamines and your risk of histamine intolerance.

- *Specific genetic variants cause underproduction of DAO and HNMT*
- *Resulting in excess histamine and ultimately histamine intolerance*

It's in your genes

The DAO and HNMT genes both encode enzymes responsible for the breakdown of histamine within your body.
• You have genetic variants in the HNMT gene associated with reduced function, meaning that you may have reduced ability to break histamines down effectively following exposure to environmental allergens.

Mast Cell Instability: Management

- Avoidance of common food triggers and allergens: **gluten, dairy, yeast**, spices, alcohol, histamine-rich and histamine-releasing foods ✅
- Avoidance of triggering **medications** (ACE inhibitors, beta blockers, NSAIDs) ✅
- Gut **microbiome** support ✅
- Stabilization with **vitamin C**, quercetin, other natural mast cell stabilizers ✅
- Optimize **vitamin D** ✅
- Restoration of circadian rhythm in MCs with **melatonin** ✅
- Investigation and management of **histamine intolerance** ✅
- Investigation and avoidance of additional environmental triggers: **mold, metals; detoxification**
- Support of **estrogen/**progesterone balance

Assessing mold: home or work

- Visual assessment
- Moisture content readings of building materials
- Surface sampling for mould
- Air sampling for mould

https://integrative-medicine.ca/detecting-mold-in-your-home-clues-to-look-for/

Detecting Mold in Your Home – Clues to Look for

by Dr. John Gannage | Nov 2, 2022 | Blog, General Wellness

If you are experiencing allergies, sinus issues, fatigue, headaches, brain fog, skin problems, or other chronic symptoms without a known cause, you may want to check your home for mold. Chronic mold exposure is an often overlooked yet common underlying problem that...

Assessing mold: urine mold toxins

[redacted]

Requisition #:	9900001	**Physician Name:**	Dr John Gannage
Patient Name:	Sample	**Date of Collection:**	Nov 24, 2021
Date of Birth:	Sep 19, 1981	**Time of Collection:**	08:00 AM
Gender:	F	**Print Date:**	Nov 30, 2021
Specimen Id.:	9900001-2		

Mycotox Profile

Creatinine Value: **190.08 mg/dl**

Metabolite	Results (ng/g creatinine)	Normal Range *	Abnormal Range
Aspergillus			
Aflatoxin-M1	15.45	< 0.5	▲ 0.5
Ochratoxin A	38.67	< 7.5	▲ 7.5
Gliotoxin	256.78	< 200	▲ 200
Penicillium			
Sterigmatocystin	12.44	< 0.4	▲ 0.4
Mycophenolic Acid	67.80	< 37.4	

Toxic metals and mast cells

- A growing body of evidence suggests that mast cells are key players in innate and adaptive immunity and *involved in autoimmune diseases*.

- Mast cells are also direct targets for autoimmunity-inducing metals both in vitro and in vivo and *play a role in the development of metal-induced autoimmune disorders*.

Assessing metals: challenge or provocation test

DOCTOR'S DATA INC

[redacted]
SEX: Female
AGE: 43 DOB: 05/19/1979

CLIENT #: 24437
DOCTOR: John Gannage MD
Markham Integrative Medicine
300 Main St N. Ground Floor
Markham, ON L3P 1Y8 Canada

Toxic Metals; urine

TOXIC METALS		RESULT µg/g Creat	REFERENCE INTERVAL	WITHIN REFERENCE / OUTSIDE REFERENCE
Aluminum	(Al)	5.0	< 25	
Antimony	(Sb)	0.078	< 0.18	
Arsenic	(As)	8.7	< 50	
Barium	(Ba)	1.1	< 5	
Beryllium	(Be)	<dl	< 0.01	
Bismuth	(Bi)	0.017	< 1	
Cadmium	(Cd)	0.61	< 0.9	
Cesium	(Cs)	7.8	< 10	
Gadolinium	(Gd)	0.02	< 0.8	
Lead	(Pb)	0.98	< 1.2	
Mercury	(Hg)	1.3	< 1.3	
Nickel	(Ni)	2.0	< 5	
Palladium	(Pd)	<dl	< 0.3	
Platinum	(Pt)	<dl	< 0.1	
Tellurium	(Te)	<dl	< 0.5	
Thallium	(Tl)	0.51	< 0.5	
Thorium	(Th)	<dl	< 0.02	
Tin	(Sn)	0.49	< 5	
Tungsten	(W)	0.048	< 0.4	
Uranium	(U)	0.005	< 0.03	

URINE CREATININE	RESULT	REFERENCE INTERVAL	-2SD -1SD MEAN +1SD +2SD
Creatinine	144	30 – 225	

SPECIMEN DATA	
Comments:	
Date Collected: 11/10/2022	**Provocation:** Pre Provocative
Date Received: 11/11/2022	**Collection Period:** Random
Date Reported: 11/17/2022	**pH upon receipt:** >8.0
Methodology: ICP-MS QQQ, Creatinine by Jaffe Reaction	

< dl: less than detection limit
Results are creatinine corrected to account for urine dilution variations. **Reference intervals are based upon NHANES (cdc.gov/nhanes) data if available, and are representative of a large population cohort under non-provoked conditions.** Chelation (provocation) agents can increase urinary excretion of metals/elements.

Assessing metals: challenge or provocation test

DOCTOR'S DATA INC.

[redacted]
SEX: Female
AGE: 43 DOB: 05/19/1979

CLIENT #: 24437
DOCTOR: John Gannage MD
Markham Integrative Medicine
300 Main St N. Ground Floor
Markham, ON L3P 1Y8 Canada

Toxic Metals; urine

TOXIC METALS		RESULT µg/g Creat	REFERENCE INTERVAL	WITHIN REFERENCE / OUTSIDE REFERENCE
Aluminum	(Al)	15	< 25	
Antimony	(Sb)	0.82	< 0.18	
Arsenic	(As)	29	< 50	
Barium	(Ba)	4.6	< 5	
Beryllium	(Be)	<dl	< 0.01	
Bismuth	(Bi)	0.11	< 1	
Cadmium	(Cd)	6.8	< 0.9	
Cesium	(Cs)	7.9	< 10	
Gadolinium	(Gd)	0.02	< 0.8	
Lead	(Pb)	30	< 1.2	
Mercury	(Hg)	17	< 1.3	
Nickel	(Ni)	12	< 5	
Palladium	(Pd)	<dl	< 0.3	
Platinum	(Pt)	<dl	< 0.1	
Tellurium	(Te)	<dl	< 0.5	
Thallium	(Tl)	0.68	< 0.5	
Thorium	(Th)	<dl	< 0.02	
Tin	(Sn)	6.0	< 5	
Tungsten	(W)	0.16	< 0.4	
Uranium	(U)	0.007	< 0.03	

URINE CREATININE	RESULT	REFERENCE INTERVAL	-2SD -1SD MEAN +1SD +2SD
Creatinine	101	30 – 225	

SPECIMEN DATA		
Comments:		
Date Collected: 11/10/2022	**Provoking Agent:** CAEDTA 3GM DMPS 195MG	**pH upon receipt:** Acceptable
Date Received: 11/11/2022	**Provocation:** Post Provocative	
Date Reported: 11/17/2022	**Collection Period:** 6 hours	
Methodology: ICP-MS QQQ, Creatinine by Jaffe Reaction		

< dl: less than detection limit
Results are creatinine corrected to account for urine dilution variations. **Reference intervals are based upon NHANES (cdc.gov/nhanes) data if available, and are representative of a large population cohort under non-provoked conditions.** Chelation (provocation) agents can increase urinary excretion of metals/elements.

Assessing estrogen dominance / hormones:

[redacted]

Last Menstrual Period:

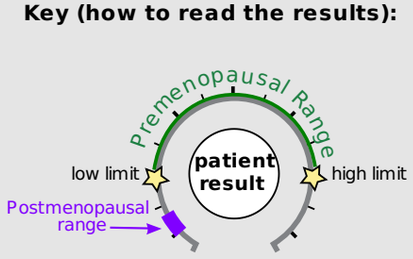
Ordering Provider:
Dr. John Gannage

DOB: 1989-10-10
Age: 26
Gender: Female

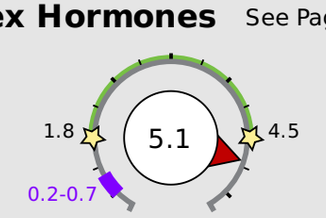
Collection Times:
2016-10-02 06:00AM
2016-10-02 08:00AM
2016-10-01 06:00PM
2016-10-01 10:00PM
2016-10-02 02:00AM

Hormone Testing Summary

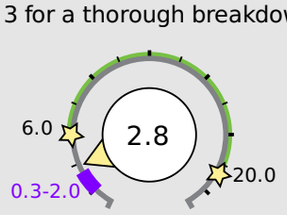
Key (how to read the results):



Sex Hormones See Pages 2 and 3 for a thorough breakdown of sex hormone metabolites

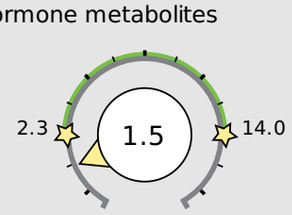


Estradiol(E2)



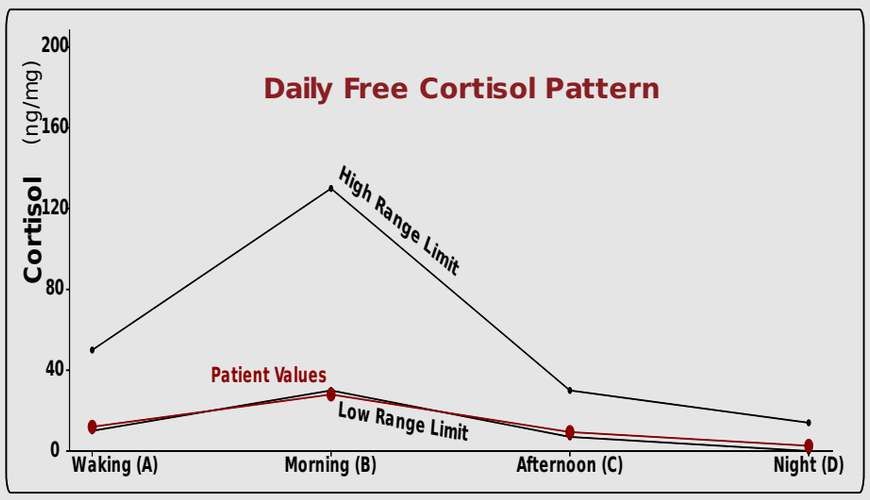
Progesterone
(Serum Equivalent, ng/mL)

Progesterone Serum Equivalent is a calculated value based on urine pregnanediol.



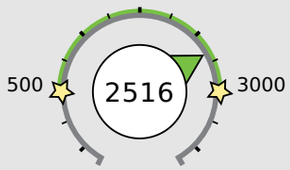
Testosterone

Adrenal Hormones See pages 4 and 5 for a more complete breakdown of adrenal hormones

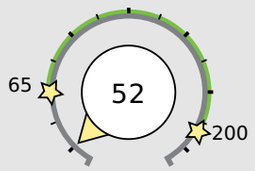


Total DHEA Production

Age	Range
20-39	1300-3000
40-60	750-2000
>60	500-1200



Total DHEA Production
(DHEAS + Etiocholanolone + Androsterone)



24hr Free Cortisol
(A+B+C+D)

cortisol metabolism

Metabolized Cortisol (THF+THE)
(Total Cortisol Production)

Free cortisol best reflects tissue levels. Metabolized cortisol best reflects total cortisol production.

Mast Cell
Why It Ma

The following videos (which can also be found on the website under the listed names along with others) may aid your understanding:
DUTCH Complete Overview **Estrogen Tutorial** **Female Androgen Tutorial** **Cortisol Tutorial**

Mast Cell Instability: Clinically Challenging

Mast Cell Instability: Clinically Challenging

- Diagnostically challenging
- Extensive process of differential diagnosis
- Frequent comorbidity with other chronic illnesses
- Lack of recognition among both conventional and alternative practitioners
- Day-to-day variability in symptoms
- High reactivity to common environmental triggers
- Intolerances often include fillers and excipients
- Neuropsychiatric symptoms are common

Poor Prognosis Indicators

Clinical findings

- Age ≥ 65 years
- Male sex
- Mastocytosis variant (cutaneous or indolent better than aggressive)
- Weight loss
- Constitutional or mediator-related symptoms
- Osteolysis
- Hepatomegaly or splenomegaly
- Portal hypertension and/or ascites
- Lymphadenopathy
- Malabsorption
- Absence of skin lesions

Serum markers

- Circulating mast cells
- Very high tryptase levels (> 200 ng/ml)
- Low albumin
- Elevated $ß_2$-microglobulin
- Ferritin > 300 µg/L
- Elevated alkaline phosphate
- Elevated aspartate aminotransferase
- Elevated lactate dehydrogenase
- Total bilirubin > 18.8 µM/L

Cytological and molecular indicators

- Cytopenias in the peripheral blood (hemoglobin < 10g/dl, platelets < 100,000/µl, neutrophils < 1000/µl), or leucocytosis
- Absolute eosinophil count ≥ 1.5 x 10^9/L
- Immature myeloid cells in the peripheral blood
- Presence of an associated clonal hematologic non-mast-cell-lineage disorder (AHNMD)
- Increased bone marrow cellularity
- Mast cell leukemia (> 20% mast cells in bone marrow smear)
- Mast cell infiltration in bone marrow > 30%
- > 5% mast cells in bone marrow smear
- > 10% immature mast cell precursors in bone marrow smear
- Marrow fibrosis grade 2+ or higher
- Abnormal karyotype
- Multilineage expression of KIT^{D816X} in the peripheral blood

Lawrence B. Afrin, Joseph H. Butterfield, Martin Raithel & Gerhard J. Molderings (2016) **Often seen, rarely recognized: mast cell activation disease – a guide to diagnosis and therapeutic options**, Annals of Medicine, 48:3, 190-201, DOI: 10.3109/07853890.2016.1161231

Mast Cells and COVID-19

Mast Cells and COVID-19

- Much of COVID-19 hyperinflammation is consistent with mast-cell-driven inflammation
- Prevalence of severe COVID-19 is similar to that of MCAS
- Drugs inhibiting mast cells (MCs) and their mediators show promise in COVID-19 [famotidine, cromolyn]
- **The dysfunctional MCs of MCAS may underlie severe acute and chronic COVID-19 illness**

Afrin, L. B., Weinstock, L. B., & Molderings, G. J. (2020). **Covid-19 hyperinflammation and post-covid-19 illness may be rooted in mast cell activation syndrome**. *International Journal of Infectious Diseases*, 100, 327-332. doi:10.1016/j.ijid.2020.09.016

Mast Cells and COVID-19

- Approximately 15-20% of COVID-19 infected patients suffer a severe form of the acute infection hallmarked by **hyperinflammatory cytokine storms causing far more morbidity and mortality than from any direct viral cytotoxicity**

- Hyperinflammatory cytokine storms in many severely symptomatic COVID-19 patients may be rooted in an **atypical response to SARS-CoV-2 by the dysfunctional MCs of MCAS rather than a normal response by normal MCs**
  - If proven, this theory has significant therapeutic and prognostic implications

- COVID-19 would be far from the first infection for which **post-infectious chronic multisystem inflammatory illness** is increasingly being suspected to be rooted in (initiation of, or more likely escalation of pre-existing) MCAS (e.g. Epstein-Barr virus infection, tick-borne infections) **rather than chronic active infection**

Afrin, L. B., Weinstock, L. B., & Molderings, G. J. (2020). **Covid-19 hyperinflammation and post-covid-19 illness may be rooted in mast cell activation syndrome**. *International Journal of Infectious Diseases*, 100, 327-332. doi:10.1016/j.ijid.2020.09.016

Mast Cells and COVID-19

- Mainly due to this extreme clinical heterogeneity and recent recognition of the existence of the disease (implying that most physicians remain unaware of it), most MCAS patients remain undiagnosed and untreated
  - Therefore their **dysfunctional MCs, whether causing mild or severe illness, are uncontrolled an**d may react inappropriately to SARS-CoV-2
- Another confounding issue is that many MCAS patients who have been undiagnosed for decades tend to minimize their problems, sometimes deceivingly declaring themselves as ‘healthy’
  - This perhaps accounts for some of the **many severe COVID-19 patients described as ‘healthy’ prior to infection**

Afrin, L. B., Weinstock, L. B., & Molderings, G. J. (2020). **Covid-19 hyperinflammation and post-covid-19 illness may be rooted in mast cell activation syndrome**. *International Journal of Infectious Diseases*, 100, 327-332. doi:10.1016/j.ijid.2020.09.016

Mast Cells and COVID-19: Obesity Link?

- **White adipose tissue from obese humans contains large numbers of mast cells**

- Serum mast cell tryptase levels are significantly higher in obese subjects than lean subjects, suggesting a role of these inflammatory cells in obesity

- CDC report: Obesity is a recognized risk factor for severe COVID-19
  - About 78% of people who have been hospitalized, needed a ventilator or died from Covid-19 have been overweight or obese
  - Possibly related to chronic inflammation that disrupts immune and thrombogenic responses to pathogens
  - Meaning: **at risk for hyperinflammatory cytokine storm**

Wang J, Shi GP. **Mast cell stabilization: novel medication for obesity and diabetes**. Diabetes Metab Res Rev. 2011 Nov;27(8):919-24. doi: 10.1002/dmrr.1272. PMID: 22069285; PMCID: PMC3318912.

Kompaniyets L, Goodman AB, Belay B, et al. **Body Mass Index and Risk for COVID-19–Related Hospitalization, Intensive Care Unit Admission, Invasive Mechanical Ventilation, and Death** — United States, March–December 2020. MMWR Morb Mortal Wkly Rep 2021;70:355–361. DOI: http://dx.doi.org/10.15585/mmwr.mm7010e4

nutrients

MDPI

Review

The Complex Interplay between Immunonutrition, Mast Cells, and Histamine Signaling in COVID-19

Sotirios Kakavas [1], Dimitrios Karayiannis [2,*] and Zafeiria Mastora [3]

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Abstract: There is an ongoing need for new therapeutic modalities against SARS-CoV-2 infection. Mast cell histamine has been implicated in the pathophysiology of COVID-19 as a regulator of proinflammatory, fibrotic, and thrombogenic processes. Consequently, mast cell histamine and its receptors represent promising pharmacological targets. At the same time, nutritional modulation of immune system function has been proposed and is being investigated for the prevention of COVID-19 or as an adjunctive strategy combined with conventional therapy. Several studies indicate that several immunonutrients can regulate mast cell activity to reduce the de novo synthesis and/or release of histamine and other mediators that are considered to mediate, at least in part, the complex pathophysiology present in COVID-19. This review summarizes the effects on mast cell histamine of common immunonutrients that have been investigated for use in COVID-19.

Keywords: immunonutrition; COVID-19; histamine

Citation: Kakavas, S.; Karayiannis, D.; Mastora, Z. The Complex

Kakavas, S.; Karayiannis, D.; Mastora, Z. The Complex Interplay between Immunonutrition, Mast Cells, and Histamine Signaling in COVID-19. *Nutrients* **2021**, *13*, 3458. https://doi.org/10.3390/nu13103458

Immunonutrition, Mast Cells and Histamine Signaling

- histamine release can be activated by numerous innate signals or exogenous **triggers including allergens, toxins, and viruses**
- **viral remnants** may prolong and exaggerate the inflammatory process, causing a histamine-induced release of more pro-inflammatory cytokines
- SARS-CoV-2 infection has been shown to activate mast cells leading to histamine release, hyper-inflammation and cytokine storm
- **immunonutrition** can be defined as modulation of either the activity of the immune system or modulation of the consequences of activation of the immune system by nutrients or specific food items fed in amounts **above those normally encountered in the diet**
- these nutraceuticals have been reported to modulate mast cell activation and histamine release with **similar potency to pharmacological interventions**

Kakavas, S.; Karayiannis, D.; Mastora, Z. The Complex Interplay between Immunonutrition, Mast Cells, and Histamine Signaling in COVID-19. Nutrients 2021, 13, 3458. https://doi.org/10.3390/nu13103458

Immunonutrition, Mast Cells and Histamine Signaling

- **Vitamin D:** preserves the stability of mast cells; in a vitamin D deficient environment, MCA occurs automatically, *even in the absence of specific triggering*
- **Vitamin E:** inhibitory effect on the proliferation, secretion, and survival of mast cells
- **Vitamin C:** patients exhibited decreased bronchial hypersensitivity to histamine and bronchoconstriction after vitamin C administration; in a recent study, 7.5 g of vitamin C administered intravenously in 89 patients with allergies or upper respiratory infections caused a significant reduction in serum histamine
- **Minerals**: Zinc; Selenium
- **Omega 3 Fatty Acids**: inhibitory effect of omega-3 PUFAs on IgE-mediated activation of mast cells
- **Flavonoids**: Quercetin; Luteolin
- **Curcumin**: reported to inhibit mast cell degranulation and histamine release in vitro and in vivo

Kakavas, S.; Karayiannis, D.; Mastora, Z. The Complex Interplay between Immunonutrition, Mast Cells, and Histamine Signaling in COVID-19. Nutrients 2021, 13, 3458. https://doi.org/10.3390/nu13103458

Summary: Key Points

Summary: Key Points

- Symptoms that we see in practice every day may be related to mast cell instability
- Different mediators may cause different symptoms (i.e. histamine —> pruritus)
- Mast cell instability exists on a spectrum
- MCAD may be suspected in cases of poorly explained chronic multi system polymorbidity, especially if inflammatory
- Patients may suffer for years/decades, see multiple practitioners, receive multiple idiopathic diagnoses before MCAD is investigated

Summary: Key Points

- Clinically challenging: diverse presentation, lack of recognition, symptom variability, high reactivity, multiple intolerances, multiple comorbidities

- Treatment approach: avoidance of triggers + control of MC mediator production/action

- Consider the use of natural mast cell stabilizers inc. vitamin C, quercetin, luteolin

- Consider the role of histamine intolerance

- COVID link should be considered