Mast Cell Activation Syndrome

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Brief Mast Cell Review

• Mast cells are a type of **white blood cell** found in connective **tissues** of the body, under the skin, near blood vessels and lymph vessels, in nerves, and in the lungs and intestines.

• Mast cells are prominent **near the boundaries between the outside world and the internal milieu**, such as the skin, mucosa of the lungs, and digestive tract, as well as the mouth, conjunctiva, and nose.

• Although best known for allergy and anaphylaxis, mast cells are involved in wound healing, angiogenesis, immune tolerance, defense against pathogens, and vascular permeability.
Disordered mast cell activation occurs when mast cells are pathologically overproduced or if their activation is out of proportion to the perceived threat to homeostasis.

**Mastocytosis**: rare and includes a variety of conditions with TOO MANY mast cells.
- Cutaneous mastocytosis
- Systemic mastocytosis
- Mast cell leukemia
- Mast cell sarcoma
- Others...

**MCAS: Mast Cell Activation Syndrome** refers to a group of disorders with diverse causes presenting with episodic multisystem symptoms as the result of [excess] mast cell mediator release.

Anaphylaxis is an extreme example of inappropriate mast cell activation.
Mast Cell Activation

• When mast cells are “activated,” inflammatory chemicals or “mediators” are released from granules. **Histamine, leukotrienes, prostaglandins** are familiar examples. **Tryptase** is the most specific for MC (but may be more difficult to detect).

• Locally activated mast cells may also send distress signals, through the nervous system and immune system, often propagating a neuroinflammatory response to other distal areas of the body.
# Table 1.

**Common Mast Cell Mediators and their Associated Symptoms.**

<table>
<thead>
<tr>
<th>Mast Cell Mediator</th>
<th>Associated Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tryptase</td>
<td>Easy bruising and bleeding, fatigue, myalgias, vertigo, flushing, diarrhea, edema</td>
</tr>
<tr>
<td>Histamine</td>
<td>urticaria, pruritis, anaphylaxis, diarrhea, angioedema, headache, hypotension</td>
</tr>
<tr>
<td>Proteoglycans</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Prostaglandin D2</td>
<td>headache, brain fog, abdominal pain, nausea, bronchoconstriction</td>
</tr>
<tr>
<td>Platelet activation factor</td>
<td>cardiac arrhythmia, bronchoconstriction, urticaria, abdominal pain</td>
</tr>
<tr>
<td>Interleukins</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Tumor necrosis factor alpha</td>
<td>fatigue</td>
</tr>
<tr>
<td>Leukotrienes</td>
<td>bronchoconstriction, mucous production</td>
</tr>
</tbody>
</table>
Mast Cell Activation/Hypersensitivity Triggers

Figure 1. Some Potential Mast Cell Triggers\textsuperscript{2-5}

- Heat, cold or sudden temperature changes
- Stress: emotional, physical, including pain, or environmental (i.e., weather changes, pollution, pollen, pet dander, etc.)
- Exercise
- Fatigue
- Food or beverages, including alcohol
- Drugs (opioids, NSAIDs, antibiotics and some local anesthetics) and contrast dyes
- Natural odors, chemical odors, perfumes and scents
- Venoms (bee, wasp, mixed vespid, spiders, fire ants, jelly fish, snakes, biting insects, such as flies, mosquitos and fleas, etc.)
- Infections (viral, bacterial or fungal)
- Mechanical irritation, friction, vibration
- Sun/sunlight

Common Symptoms of MCAS

- **Anaphylaxis**
- **Dermatological**
- **Cardiovascular**
- **Gastrointestinal**
- **Respiratory**

**MAS T CELL MEDIATOR SYMPTOMS**

- Anaphylaxis
- Flushing of the face, neck, and chest
- Itching, +/- rash
- Hives, skin rashes
- Angioedema (swelling)
- Nasal itching and congestion
- Wheezing and shortness of breath
- Throat itching and swelling
- Headache and/or brain fog, cognitive dysfunction, anxiety, depression
- Diarrhea, nausea, vomiting, abdominal pain, bloating, gastroesophageal reflux disease (GERD)
- Bone/muscle pain, osteosclerosis, osteopenia, osteoporosis
- Light headedness, syncope/fainting
- Rapid heart rate, chest pain
- Low blood pressure, high blood pressure at the start of a reaction, blood pressure instability
- Uterine cramps or bleeding


7/26/2022
Clinical criteria for mast cell activation syndrome

1) Episodic symptoms consistent with mast cell mediator release affecting **two or more organ systems** evidenced as follows:

- **Skin**: urticaria (hives), angioedema (sudden swelling), flushing, dermatographia
- **Gastrointestinal**: nausea, vomiting, diarrhea, abdominal cramping
- **Cardiovascular**: hypotensive syncope (fainting), tachycardia
- **Respiratory**: wheezing
- **Naso-ocular**: conjunctival injection, pruritus (itching), nasal stuffiness
Clinical criteria for mast cell activation syndrome

2) Improved symptoms after treatment with:

• H1 (antihistamines) and H2 (famotidine) histamine receptor antagonists
• Leukotriene antagonists: montelukast
• Mast cell stabilizers – cromolyn sodium, ketotifen (also an antihistamine)
CLINICAL CRITERIA FOR MAST CELL ACTIVATION SYNDROME

3) Elevation of a validated urinary or serum marker of mast cell activation:
   • Total serum tryptase (very specific for mast cells)
   • Plasma prostaglandin D2, histamine
   • Biopsy tissue (i.e. GI tissue) with staining positive for increased numbers of mast cells (CD 117 staining)
   • 24-hour urine levels of:
     • N-methylhistamine
     • 11B-Prostaglandin F2α (11B-PGF2α)
     • Leukotriene E4 (LTE4)

REMEMBER: Empiric trials of therapy when there is a clinical suspicion for MCAS can also be diagnostic!
Relevance of MCAS to Our Topic?

The acute COVID-19 “cytokine storm” is characterized by rapid proliferation and hyperactivation of T cells, macrophages, and natural killer cells, and the overproduction of >150 inflammatory cytokines and chemical mediators released by immune or nonimmune cells. Mast cells (MCs) are activated by SARS-CoV-2.


Relevance of MCAS to Long COVID or ME/CFS

- **Questionnaires** were given to:
  - 136 Long COVID
  - 136 Healthy Controls
  - 80 MCAS patients (5 systems)


**Mean Mast Cell Mediator Release Syndrome** scores for each group with whiskers showing 95% confidence intervals.


Figure 3
Spider web plots of mean mast cell mediator release syndrome scores.
Mast cell-associated disease-specific pain syndromes, mast cell activation and its common activators:

- Migraine
- Chronic prostatitis
- Endometriosis
- Bladder pain syndrome
- Fibromyalgia
- Resting mast cell
- Activated mast cell releasing mediators
- Cancer
- Sickle cell disease
- Post-operative pain
- Irritable Bowel Syndrome

**Mast cell disease**

- Self-injurious behavior
- Venom-induced
- Vulvodynia

**Chemokines**

- C3α, C5α
- CGRP, SP, CRH
- NGF, SCF
- Trypsin, trypsinase
- Venoms

**Vasoactive intestinal peptide**

- Estrogens
- IgE, IgG1

**Activating factors**

- ATP

**Consequences**

- Neuropathic pain
Mast Cell Disease
Coexisting Conditions

- Interstitial Cystitis (Bladder Pain Syndrome)
- Rheumatoid arthritis
- Chronic Fatigue Syndrome (ME/CFS)
- Restless Leg Syndrome
- Multiple Sclerosis
- Osteopenia/Osteoporosis
- Osteoarthritis
- Eosinophilic esophagitis
- Fibromyalgia
- Idiopathic Anaphylaxis
- Diabetes
- Ehlers-Danlos
- Dysautonomia
- Multiple Chemical Sensitivity

MastCellDisease.com
Abnormal laboratory testing refers to those with POTS whose laboratory workup suggested elevated MCAS-related serum and urine mediators.
**Table 2**
Comparison of Symptoms in 44 Patients Who Underwent Laboratory Testing

<table>
<thead>
<tr>
<th>Abnormal Values</th>
<th>POTS-like With Atypical Symptoms</th>
<th>POTS Alone</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=29)</td>
<td>(n=15)</td>
<td></td>
</tr>
<tr>
<td>ESR or</td>
<td>6/28* (21%)</td>
<td>3/14* (21%)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>CRP abnormal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tryptase</td>
<td>2/23* (9%)</td>
<td>0/9* (0%)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Prostaglandin</td>
<td>16/28* (57%)</td>
<td>0/15 (0%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Histamine</td>
<td>17/29 (59%)</td>
<td>0/15 (0%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>or</td>
<td>23/29 (79%)</td>
<td>0/15 (0%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>methylhistamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abnormal</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
• Nociceptive inputs from these primary afferent fibers signaling peripheral inflammation or other noxious stimuli are relayed through the dorsal root ganglion (DRG) into the spinal dorsal horns

• These signals are then transmitted to second-order neurons in the trigeminal nucleus caudalis (TNC) within the brainstem


• The trigeminal nuclear complex (including the trigeminal nucleus caudalis (TNC) and its related extensions at C1-C2) then send afferent signals to second order neurons.

• This signaling is often through trigeminal neuron release of substance P and CGRP acting upon meningeal vessels of the trigeminovascular system and upon dural mast cells.

• This activation can lead to triggering or propagation of migraine and of central pain sensitization.
Mast Cell Activation Treatments

- Low Histamine Diet
- Diamine oxidase (reduce histamine levels in foods)
- H1 Blockade (fexofenadine, loratadine, cetirizine, levocetirizine)
- H2 Blockade (famotidine, ranitidine, cimetidine)
- Benadryl (diphenhydramine)
- Leukotriene Blockade (montelukast)
- Mast Cell Stabilizers
  - Liquid cromolyn/Gastrocrom (1 mL or 20 mg up to 5 ml or 100 mg 15 minutes before meals and medications)
  - Compounded cromolyn sodium (200 mg po tid to qid)
  - Compounded ketotifen (1 mg po bid)
  - OTC Quercetin
  - Anti-IgE biologics (omalizumab/Xolair)

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