Few or No Allergies, but Still Reacting

UNDERSTANDING MAST CELL ACTIVATION DISORDER

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Mast Cell Activation Disorder/ Syndrome is
(MCAD/MCAS)

“ A collection of disorders characterized by...

- Accumulation of pathological mast cells in potentially any or all organs and tissues

or

- Aberrant release of variable subsets of mast cell mediators, leading to one of more symptoms, that come and go -
  - Flushing / Itch / Hives (Urticaria) / Swelling (angioedema)
  - Tachycardia (Fast Heart Rates)
  - Presyncope (nearly fainting), syncope (Fainting/Loss of Consciousness)
  - Irritable bowel like symptoms -Abdominal Pain /Diarrhea/Constipation / Bloating
  - Cough/ Wheeze/Reactive Airway/Difficulty Breathing
Age of Immune Dysregulation
The Increased Burden of Autoimmune and Allergic Disorders

Adapted from Bach, NEJM 2002
20-40% of children and adults living in industrialized nations are affected by immediate hypersensitivity/allergic disorders.
More than Histamine Intolerance

Mast-Cell Activators
Allergens, bacteria, cytokines, drugs, fungi, peptides, toxins, and viruses

Cardiovascular
- Hypotension
- Syncope or near syncope
- Light-headedness
- Tachycardia

CRH, chymase, histamine, interleukin-6, PAF, renin, TNF, tryptase

CRH, histamine, interleukin-6, TNF

Systemic
- Fatigue
- Generalized malaise
- Weight loss

CRH, histamine, interleukin-6, tryptase

Respiratory
- Nasal congestion
- Nasal pruritus
- Shortness of breath
- Throat swelling
- Wheezing

CRH, histamine, interleukin-6, neurotensin, PAF, PGD₂, serotonin, TNF, tryptase, VIP

CRH, histamine, interleukin-6, tryptase

Histamine, interleukin-6, CysLTs, PAF, PGD₂

Musculoskeletal
- Aches
- Bone pain
- Osteopenia
- Osteoporosis

Interleukin-6, PGD₂, RANKL, TNF, tryptase

Digestive
- Abdominal cramps
- Diarrhea
- Esophageal reflux
- Nausea and vomiting

CRH, histamine, interleukin-6, neurotensin, PAF, PGD₂, serotonin, TNF, tryptase

Neurologic
- Anxiety
- Depression
- Decreased concentration and memory
- Insomnia
- Migraines
Mast Cells are situated in every organ system and have various sensors to detect different "dangers." The kind of trigger and the site of encounter will determine which chemical mediators are released, and consequently, the MCAD associated symptoms.

- **Nasal Congestion**
- **Nasal Itch**
- **Shortness of Breath**
- **Throat Swelling**
- **Wheezing**
- **Body Aches**
- **Bone Pain**
- **Premature Osteoporosis/Osteopenia**
- **Nasal Congestion, Nasal Itch Shortness of Breath Throat Swelling Wheezing**
- **Burning Sensation/Pain, Urinary Frequency**
- **Feeling Fatigue**
- **Weight Loss**
- **Weight Gain**
- **Malaise**
- **Flushing**
- **Itch**
- **Hives**
- **Swelling**
- **Bloating**
- **Cramps**
- **Heartburn**
- **GERD**
- **Nausea**
- **Vomiting**
- **Malaise Weight Loss Weight Gain Fatigue**
- **Prostaglandins (PGs)**
- **Platelet Activating Factor (PAF)**
- **Interleukin-6 (IL-6)**
- **Tumor Necrosis Factor (TNF)**
- **Histamine**
- **Corticotropin Releasing Hormone (CRH)**
- **Fast Heart Rate/Palpitations**
- **Dizziness/Lightheadedness**
- **Low Blood Pressure**
- **Anxiety/Depression**
- **Brain Fog/Poor Concentration**
- **Headache Syndromes**
- **Sleep Disorders**
- **Flushing**
- **Itch**
- **Hives**
- **Swelling**
- **Bloating**
- **Cramps**
- **Heartburn**
- **GERD**
- **Nausea**
- **Vomiting**
- **Body Aches**
- **Bone Pain**
- **Premature Osteoporosis/Osteopenia**
- **Respiratory**
- **Skeletal**
- **Urogenital**
- **Endocrine**
- **Digestive**
- **Arterial**
- **Nervous**
- **Integumentary**
Mast Cell Activation Syndrome (MCAS): a collection of disorders characterized by...

- Accumulation of pathological mast cells in potentially any or all organs and tissues
- Aberrant release of variable subsets of mast cell mediators, leading to one of more symptoms (suggestive of systemic mast cell degranulation)
Proposed Criteria for MCAS Diagnosis

(1) Episodic Signs & Symptoms Consistent with Mast Cell (MC) Activation, affecting 2 or more organ systems

(2) Response to therapy – decrease in frequency, severity or resolution of symptoms with anti-MC mediator therapies or MC stabilizers
Proposed Criteria for MCAS Diagnosis

(3) Evidence of an increase in validated urinary or serum markers of MC activation; increased burden of tissue mast cells (CD117) or chronically activated mast cells (CD117+ and CD25+/CD2+/CD30+)

(4) Rule out Primary MCAS and Secondary Causes of MC activation, clinical entities that mimic MC activation
MCAD Criteria #1

Episodic Signs & Symptoms Consistent with Mast Cell (MC) Activation, affecting 2 or more organ systems

1. Episodic Signs & Symptoms Consistent with Mast Cell (MC) Activation, affecting 2 or more organ systems

- Light-headedness * Breathing Troubles* Lightheadedness/ Passing Out, Low Blood Pressure * Shock * ASTHMA Loss of Consciousness * Itchy Skin * Hives * Skin swelling * Warm, Red, Fleeting Rashes * Stomach Troubles RHINITIS Sneezing * Congestion * Stiffness * Itchy nose * ANAP...
Skin (80-90% reactions)
Hives (Urticaria), Itch
Flushing, Swelling
(Angioedema)
Mucosa
Itch, swelling –
lips, tongue, mouth)

Brain (> 20% reactions)
Sense of uneasiness
Headache
Dizziness
Confusion
Tunnel Vision

Heart, Blood
Pressure (10-45 %
reactions)
Chest Pain
Fast Heart Rate,
Palpitations (pounding)
Weak pulse
Dizziness
Fainting

Joint and Muscle Pain

Airway (70% reactions)
Throat Tightening, swelling
Lungs = chest tightness,
wheeze,
can’t take a deep breath

Gastrointestinal tract
(30-45% reactions)
Nausea
Cramping
Abdominal Pain
Vomiting
Diarrhea

Genito-Urinary tract
(>10% reactions)
Uterine Cramping
Swelling -labia
# Mast Cell Activation Disorder: Signs and Symptoms

## Mastocytosis

(Escribano et al, JACI 124:514)

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<th>Skin Lesions</th>
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<td>Pruritis</td>
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<td>Diarrhea</td>
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<td>Abdominal Cramping</td>
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<td><strong>Neuropsychiatric Symptoms</strong></td>
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<tr>
<td>Anaphylaxis</td>
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<td>Peptic Symptoms</td>
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<td>Hepatomegaly</td>
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<td>Splenomegaly</td>
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## Nonclonal Mast cell activation disorder

(hamilton, jaci 128;147)

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<td>Flushing</td>
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<td><strong>Neuropsychiatric</strong></td>
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<td>Diarrhea</td>
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<td>Rhinitis (Naso-ocular)</td>
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<tr>
<td>Asthma</td>
<td>39%</td>
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<tr>
<td>Anaphylaxis</td>
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</table>
Mast Cell Secretagogues/Activators

- **MC = Effectors cells for immediate hypersensitivity reactions**
  - IgE-FcRe crosslinking
  - Anaphylatoxins (C3a, C5a)
  - Aggregated IgG

- **MC = Front Line Defense**
  - Toll Like Receptors – bacteria, viruses, parasites
  - **Toxins, venoms**
MCAD Criteria #2

Response to therapy – decrease in frequency, severity or resolution of symptoms with anti-MC mediator therapies or MC stabilizers
Response to Treatment: Targeting MC/MC Inflammatory Mediators

**Immediate Release**
- Granule contents: Histamine, TNF-α, Proteases, Heparin
- Sneeze
- Nasal congestion
- Itchy, runny nose
- Watery eyes

**Over Minutes**
- Lipid mediators: Prostaglandins, Leukotrienes
- Wheezing
- Bronchoconstriction

**Over Hours**
- Cytokine production: Specifically IL-4, IL-13
- Mucus production
- Eosinophil recruitment

**Histamine Blockade**
- Tricyclic Agents

**Leukotriene Blockade**

**Anti-IGE mAb**

**Traditional Chinese Herbal Medicine**

**Corticosteroids**

**MC stabilizers**
Emergency Response Plan for Patients with MCAD

WHAT TO SAY UPON ARRIVING IN THE EMERGENCY ROOM:

If your problem is a full blown “mast cell attack”, ”mast cell degranulation”, fainting, anaphylaxis:

I am ___ years old with a known systemic mast cell disorder, and I am having anaphylaxis.

(Say this even if you have not experienced anaphylaxis before as any mast cell degranulation attack can result in full blown anaphylaxis.)

Anaphylaxis Kit
- epinephrine
- histamine blockade (H1 and H2 blocker)
- Corticosteroids (hydrocortisone or methylprednisolone)
## Quick Reference Guide:

### Medications to Use and Avoid in Patients with MCAD

<table>
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<tr>
<th>MEDICATION TYPE</th>
<th>AVOID THESE DRUGS</th>
<th>DRUGS THAT MAY BE TOLERATED</th>
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</thead>
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<tr>
<td>GENERAL DRUGS</td>
<td>Alcohol</td>
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<td></td>
<td>anticholinergic drugs</td>
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<td>Dextran</td>
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<td>Dextromethorphan</td>
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<td>Polymyxin B</td>
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<td>Quinine</td>
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<td>Beta-adrenergic blockers</td>
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<td>Tramadol</td>
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<td></td>
<td>NSAIDs **</td>
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</table>

**may be tolerated by some individuals

The Mastocytosis Society.  www.tmsforacure.org
## Medications to Use and Avoid in Patients with MCAD

<table>
<thead>
<tr>
<th>MEDICATION TYPE</th>
<th>AVOID THESE DRUGS</th>
<th>DRUGS THAT MAY BE TOLERATED</th>
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<td>Muscle Relaxants</td>
<td>Atracurium</td>
<td>Pancuronium</td>
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<td>Vercuronium</td>
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<td>D-tubocurarine</td>
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<td>Metocurine</td>
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<td></td>
<td>Mivacurium</td>
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<td></td>
<td>Succinylcholine</td>
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<td>Local Anesthetics</td>
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<td>Propofol</td>
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<tr>
<td>Inhaled Anesthetics</td>
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<td>Sevoflurane</td>
</tr>
</tbody>
</table>
Emergency Response Plan for Patients with MCAD

Anaphylaxis Kit
- epinephrine
- histamine blockade (H1 and H2 blocker)
- Corticosteroids (hydrocortisone or methylprednisolone)
- Supplemental oxygen
- Short acting beta-agonist

Medications to be Avoided:
- Nonsteroidal anti-inflammatory medications
- Morphine, codeine derivatives
- Vancomycin

Pre-medication before surgery/
minor procedure
Prednisone, 24 hours and 1—2 hours prior to surgery
- diphenhydramine or hydroxyzine,
12 hr and 1 hour prior to surgery
- ranitidine or famotidine
12 hr and 1 hour prior to surgery
- montelukast 1 hour prior to Surgery

If the patient presents with flushing, rash, hives, swelling, abdominal pain, nausea, vomiting, shortness of breath, wheezing or hypotension, respond with the following:

Administer
* Epinephrine 0.3 cc of 1/1000 and repeat 3x at 5-minute intervals if BP < 90 systolic (0.1 cc for children under 12)
* Benadryl (Generic: diphenhydramine) 25-50 mg (12.5-25 for children under 12) orally, intramuscular or intravenously every 2–4 hours or Atarax (Generic: hydroxyzine) 25mg (12.5 mg for children under 12) orally every 2–4 hours
* Solu-Medrol (Generic: methylprednisolone) 120 mg (40 mg for children under 12) IV/IM
* Oxygen by mask or nasal cannula 100%
* Albuterol nebulization

Call 911 and take the patient to the closest Emergency Room.

Pre-medication for major and minor procedures and for radiology procedures with and without dyes:
* Prednisone 50 mg orally (20 mg for children under 12) 24 hours and 1—2 hours prior to surgery
* Benadryl (Generic: diphenhydramine) 25-50 mg orally (12.5 mg for children under 12) or Atarax (Generic: hydroxyzine) 25 mg orally, 1 hour prior to surgery
* Zantac (Generic: ranitidine) 150 mg orally (20 mg for children under 12) 1 hour prior to surgery
* Singular (Generic: montelukast) 10 mg orally (5 mg for children under 12) 1 hour prior to Surgery

Drugs to be avoided:
* Aspirin and non-steroidal anti-inflammatory medications
* Morphine, codeine derivatives
* Vancomycin

Recommends: Tylenol

The Mastocytosis Society thanks Dr. Mariana Castells for this emergency protocol.
Laboratory Tests to Run in the Emergency Department when treated for MCAD “attack”/ Anaphylaxis

1. Serum Tryptase—upon arrival in the ER and three hours later.
2. 24 hour urines for:
   - n-methyl histamine
   - prostaglandin D2 (PGD2)
   - prostaglandin 11 beta F2A (BPG-F2A)
3. Complete chemistry panel
4. CBC with differential

You MUST have your allergist or primary care provider sign the bottom of this form stating that he or she will be responsible for the follow-up on the 24 hour urine collections. Otherwise, the ER physicians will be reluctant to order them since they cannot be sure of follow-up care. Remember to contact your physician for follow-up after discharge.
MCAD Criteria #3

Laboratory Evidence reflecting recurrent, aberrant MC Activation
Measuring MC Activation, Activation Markers, Inflammatory Mediators

Pathology - spindle, MC, MC aggregates

Serum, Tryptase

CD2, CD30, CD25 Expression

Immediate Release
Granule contents:
Histamine, TNF-α, Proteases, Heparin
Sneezing
Nasal congestion
Itchy, runny nose
Watery eyes

Over Minutes
Lipid mediators:
Prostaglandins
Leukotrienes
Wheezing
Bronchoconstriction

Over Hours
Cytokine production:
Specifically IL-4, IL-13
Mucus production
Eosinophil recruitment

Histamine, PGD2, 11-beta PGF2

Serum, Urine Histamine
Maybe.
Other Conditions That Can Mimic Mast-Cell Disorders.

**Cardiac conditions:** Coronary hypersensitivity (the Kounis syndrome)* Postural orthostatic tachycardia syndrome

**Endocrine conditions:** Fibromyalgia Parathyroid tumor Pheochromocytoma Carcinoid syndrome

**Digestive conditions** Adverse reaction to food* Eosinophilic esophagitis* Eosinophilic gastroenteritis* Gastroesophageal reflux disease; Gluten enteropathy; Irritable bowel syndrome; Vasoactive intestinal peptide–secreting tumor

**Immunologic conditions:** Autoinflammatory disorders such as deficiency of inter- leukin-1–receptor antagonist*; Familial hyper-IgE syndrome Vasculitis*

**Neurologic and psychiatric conditions** Anxiety; Chronic fatigue syndrome Depression; Headaches; Mixed organic brain syndrome; Somatization disorder; Autonomic dysfunction;Multiple sclerosis

**Skin conditions:** Angioedema* Atopic dermatitis* Chronic urticaria* Scleroderma*
Two types of MCAD

Proliferative MCAD

Nonproliferative MCAD
## Classification of MC Activation Disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Primary</strong></td>
<td>Symptoms Associated with monoclonal mast cell population</td>
</tr>
<tr>
<td></td>
<td>A. Mastocytosis</td>
</tr>
<tr>
<td></td>
<td>B. Monoclonal Mast Cell Activation Syndrome (MMAS)</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td>A. Allergic (IGE mediated) Disorders</td>
</tr>
<tr>
<td></td>
<td>B. Mast Cell activation associated with chronic inflammatory or Neoplastic disorders</td>
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<td></td>
<td>C. Physical Urticaria</td>
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<td></td>
<td>D. Chronic Autoimmune Urticaria</td>
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<tr>
<td><strong>Idiopathic</strong></td>
<td>A. Anaphylaxis</td>
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<td></td>
<td>B. Angioedema</td>
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<tr>
<td></td>
<td>C. Urticaria</td>
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<td>D. MCAS</td>
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Spectrum of Mast Cell Disorders: primary vs. secondary

adapted from Akin et al, JACI

1. Typical MC mediated clinical symptoms

2. Transient/sustained increase in MC mediators, e.g. tryptase**

3. Response to anti-MC/MC- mediator treatment(s)

**Decreased likelihood MMAS, SM or MCL by bone marrow MC aggregates diminishes significantly in those with tryptase < 20 ng/mL

Primary MCAS

<table>
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<tr>
<th>MMAS</th>
<th>SM</th>
<th>MCL</th>
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</table>

Secondary or Idiopathic MCAS

MAST CELL PROLIFERATION
Systemic Mastocytosis

- **Systemic Mastocytosis** =
  - 1 major + 1 minor criteria
  - 3 Minor Criteria

- **Major**: Multifocal, dense aggregates of mast cells in bone marrow

- **Minor Criteria**
  - > 25% MC = atypical morphology (spindle shaped)
  - CD2+ and/or CD25+ mast cells
  - KIT D816V mutation (activating) in Bone Marrow Bx
  - Baseline serum tryptase > 20 ng/ml

Figure 2: Typical bone marrow histology and immunohistochemistry for systemic mastocytosis with compact mast cell infiltrates (patient no. 54; e+f), as depicted by hematoxylin-eosin (a), anti-trypase (b), anti-CD117 (c), and anti-CD25 (d and e) immunohistochemical stainings for mast cells. The compact mast cell infiltrates were stained with 95% formic acid for 5 min (f) and 160°C for 30 sec to enhance detection of mast cells by laser pressure catapulting (g–i) as well as aspirate smears, increased amounts of cytoplasmic projections (arrowheads; j–l) as well as degranulation of the cytoplasm (arrowheads; m–o). Original magnification ×63.
Mast Cell Activation Disorders in Context of other Disorders- “secondary MCAD”

- Allergic or IGE mediated Disorders
- Primary Immunodeficiencies or Neoplastic disorders
- Chronic Autoimmune Urticaria
- Physical Urticaria (*Connective Tissue Disorders??*)

![Diagram showing mast cell with eosinophils, fibroblasts, lymphocytes, and nerve fibers.]
Some things appear to be here on earth to help us understand how things work...and go wrong (like peanut allergy). When we look at EDS, we see some interesting things like the extremes of what goes wrong when collagen gets screwed up.
Have you .... wondered why (some) generally rupture cruciate ligaments during a certain time of their lives, about the same time that (others) are blowing discs, developing heart murmurs, and suffering from immune mediated diseases and that first big wave of cancer? Haven’t you seen patterns that beg answers, like the same (patients) having this happen and even the same time of year? Yes, I had three cruciate ligament injuries come in the same week last month. Hmmmm...”Coincidence”? I don’t think so. Why do they rupture those in one leg and then six months or a year, sometimes to the day, they blow the other? That’s the pattern we see in almost all immune mediated diseases of tissue, whether it be the eyes, neurological system, and even the kidneys. ...How about the ones that do it the earliest in their lives?
And what breeds of dogs are involved? It’s the dogs that are the most food allergic, isn’t it? (Labs, Cockers, Poodles, Rotties, Labs again, English bulldogs, Bichons, Cavaliers...the usual suspects).

Which of these groups (of patients) have the worst
- cruciate ligament ruptures,
- back problems,
- heart valve problems
- combination of gastric motility disorders
- weakened supportive ligaments
- food intolerance/allergies are secondary to mucosal damage, a condition known as the “leaky gut syndrome”

(These) patterns we see...should tell us so much and can help sort out the cause-and-effect, (the) relationships that...often get completely wrong
It is now emerging as a multi-systemic disorder with widespread manifestations...

Castori, Dermatology 2012
Determine prevalence of mast cell activation syndrome among Ehlers-Danlos patients.

- Patients with confirmed diagnosis of EDS-JHS, by geneticist or rheumatologist were identified at our clinical allergy/immunology practice.

- Retrospective chart review to obtain symptoms, medications, spirometry/serial peak flow measurements, lab results.

- Validated questionnaires distributed:
  - Rhinitis
  - Urticaria
  - Asthma
  - Anaphylaxis

- Descriptive statistics used for analysis.
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## Results

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<tr>
<th>Subtype</th>
<th>Inheritance</th>
<th>Gene (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>AD</td>
<td>COL5A1, COL5A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypermobility/JHS</td>
<td>AD??</td>
<td>Mostly unknown</td>
</tr>
<tr>
<td>Vascular</td>
<td>AD</td>
<td>COL3A1</td>
</tr>
<tr>
<td>Kypho-scoliotic</td>
<td>AR</td>
<td>PLOD1</td>
</tr>
<tr>
<td>Arthrochalasia</td>
<td>AD</td>
<td>COL1A1, COL1A2</td>
</tr>
<tr>
<td>Dermatosparaxis</td>
<td>AR</td>
<td>ADAMTS2</td>
</tr>
</tbody>
</table>

- All patients had EDS-HJS confirmed by a geneticist, physiatrist or rheumatologist.
- 6 adults, 31 to 53 years of age.
- 3 children, 5 to 9 years of age.
- 67% female (6 patients).
7 patients (78%) had chronic rhinitis symptoms, nasal congestion, over the past month.
- Majority with symptoms severe enough to interfere with sleep.

All patients reported rhinitis symptoms that were controlled on anti-mediator therapy:
- Anti-histamine
- Mast cell stabilizer
- Leukotriene modifier

100% of patients reported pruritus over past month.
- Majority (89%) had hives

Children had hives/itch more frequently in an average week than adults.

7 patients (78%) used anti-histamines to control their skin symptoms.
<table>
<thead>
<tr>
<th>Anaphylaxis</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 patients (78%) reported previous symptoms highly likely to be anaphylaxis based on clinical diagnostic criteria:</td>
<td>7 patients (78%) had a history of asthma.</td>
</tr>
<tr>
<td>• acute onset of illness</td>
<td>• All patients with a history of asthma were treated with a rescue inhaled beta-agonist.</td>
</tr>
<tr>
<td>• either spontaneous or after exposure to common MC triggers</td>
<td>• 44% were on an inhaled corticosteroid, 78% were on a leukotriene modifier.</td>
</tr>
<tr>
<td>• involving skin, mucosal tissue, hypotension, and respiratory and gastrointestinal symptoms.²</td>
<td></td>
</tr>
</tbody>
</table>
## Results: MCAS Criteria

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>6</td>
<td>54</td>
<td>10</td>
<td>7</td>
<td>50</td>
<td>34</td>
<td>43</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>F</th>
<th>M</th>
<th>F</th>
<th>M</th>
<th>F</th>
<th>M</th>
<th>F</th>
<th>F</th>
<th>F</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Episodic Symptoms</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Improved with anti-MC mediators</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Tryptase</th>
<th>1</th>
<th>&lt;10</th>
<th>&lt;10</th>
<th>&lt;10</th>
<th>&lt;10</th>
<th>&lt;10</th>
<th>&lt;10</th>
<th>&lt;10</th>
<th>&lt;10</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Other diseases ruled out</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
</tr>
</thead>
</table>
Results: Labs

- 7 of the 9 patients had no objective signs of IgE-mediated allergy, using in vitro and/or in vivo, percutaneous skin testing.

- Among these patients, the total serum serum IGE level ranged from undetectable to 101 KIU/ml (Quest Diagnostics), with the 78% had IGE < 10 KIU/ml
Case Series: Meeting the Proposed Criteria for MCAS Diagnosis?

1. Episodic Symptoms Consistent with Mast Cell (MC) Activation
   - 9 of 9 patients = skin, GI, CV, respiratory

2. Response to therapy – decrease in frequency, severity or resolution of symptoms with anti-MC mediator therapies or MC stabilizers
   - All 9 patients needed at least 2 classes of anti-MC therapies to control symptoms, and
   - 7 of 9 required rescue B-agonist therapy for acute respiratory or CV distress (albuterol, epinephrine)
Case Series: Meeting the Proposed Criteria for MCAS Diagnosis?

- (3) Evidence of an increase in validated urinary or serum markers of MC activation
  - In NY state, only serum tryptase and 24 hr urine histamine are available, all 9 patients had serum tryptase < 10 IU/ml
  - Decreased likelihood MMAS, SM or MCL by bone marrow MC aggregates diminishes significantly in those with tryptase < 20 ng/mL (Akin et al, 2011)
  - 24 hour urine collection to measure prostaglandin D2 (not available in NY state)
Case Series: Meeting the Proposed Criteria for MCAS Diagnosis?

(4) Rule out Primary and Secondary Causes of MC activation, established clinical entities that trigger or mimic MC activation

- Patients often undergo multiple medical evaluations by different physicians without a definitive diagnosis.
Conclusion: Patients “Living in Plain Sight” undiagnosed with MCAD

- EDS-JHS patients appear to display non-IgE-mediated MC activation
  - Asthma, Anaphylaxis, Rhinitis, IBS, Drug Sensitivities, Food Sensitivities, Mood Disorders

- All of the patients “met” 3 of the 4 proposed diagnostic criterion for mast cell activation syndrome
  - MC mediated symptoms
  - These symptoms were best controlled by combination anti-mediator therapy, MC stabilizers as well as avoidance measures (environmental and food)
  - Validated urinary or serum marker of mast cell activation
  - None of the patients met all of the proposed criteria for monoclonal mast cell activation syndrome

Future Directions

Help elucidate the mechanism(s) of IGE and non-IgE-mediated MC activation.

Abnormal collagen metabolism $\leftrightarrow$ mast cell activation?
Classification of these EDS-JHS patients = Secondary MCAS

<table>
<thead>
<tr>
<th>Primary</th>
<th>Symptoms Associated with monoclonal mast cell population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A. Mastocytosis</td>
</tr>
<tr>
<td></td>
<td>B. Monoclonal Mast Cell Activation Syndrome (MMAS)</td>
</tr>
</tbody>
</table>

| Secondary | A. Allergic (IGE mediated) Disorders |
|           | B. Mast Cell activation associated with chronic inflammatory or Neoplastic disorders |
|           | C. **Physical Urticarias/Systemic Hypersensitivity Reactions = Inherited Connective Tissue Disorders** |
|           | D. Chronic Autoimmune Urticaria                      |

| Idiopathic | A. Anaphylaxis |
|            | B. Angioedema |
|            | C. Urticaria  |
|            | D. MCAS      |
Dysfunctional communication between MC-surrounding connective tissue = increased mast cell activation?

There are few reports on the cross talk between different components of the innate immune=epithelial barrier & immune cells

- Abonia et al, 2013: Hypothesized abnormal interaction between mutated collagen COL5A1 and excess TGFβ-1 for EoE pathogenesis
- Filaggrin


