Living with Mast Cell Activation Syndrome

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Got MCAS?
Mast Cell mediated disorders are common

- 1 out of 2 of us are coping with some chronic immune mediated disorder.
  - ‘allergies’ (rhinitis), sinus infections, hives (urticaria), food allergy/intolerance, skin swelling (angioedema), eczema (atopic dermatitis and contact dermatitis), asthma issues, and the prototype of immediate hypersensitivity syndromes, anaphylaxis

Anaphylaxis Signs and Symptoms
Why the rise in hypersensitivity disorders? Our genes in this environment!

The human race has come to dominate its environment so completely that any analysis of the increase or appearance of a disease has to take changes in our lifestyle into account. In the case of allergic disease [hypersensitivity disorders] changes in our environment, diet, water quality, and personal behavior over the last 150 years have played a dominant role in the specificity of these diseases, as well as in prevalence and severity...

it is clear that the consequences of hygiene, indoor entertainment, and changes in diet or physical activity have never been predicted.

Thomas A. E. Platts-Mills, MD, PhD, FRS,
Connective Tissue Disorder
PIDD
Autoimmune Dz.
Mastocytosis
Hypertryptasemia
Atopic Disorders

Why?

- Trauma
- Stress
- Infection
- Chemical exposure
  - manufactured
  - mold
  - mycotoxins (naturally occurring)
But most patients with MCAD suffer for years...

It is very common for one hypersensitivity condition to progress/morph into another, be provoked by more triggers. Consider the “allergic march”:

Yet most children and adults, with reactions to substances in foods and medications, in the air, or in lotions/creams applied to our skin, report not

- feeling better with available treatments, and
- suffering with other illnesses that travel with these chronic hypersensitivity disorders.

Mast cell activation syndrome is easily treated, if it’s recognized

Patients with mast cell activation syndrome (MCAS) frequently go for years without an accurate diagnosis... Harding, Reuters Health-New York, 2011

- Asthma
- Eczema
- Rhinitis

Urticaria/Angioedema: can occur at any age and can last for weeks or years for some

- Sleep Disorders: Tossing and turning all night due to hay fever?
- Why Seasonal Allergies Cause 'Brain Fog' -- Here's What The Science Says
- Sad in the spring? Allergy-mood link is real
Medically speaking, they are not serious cases as regards prospective death, but they are often extremely serious as regards prospective life. Their symptoms will rarely prove fatal, but their lives will be long and miserable, and they may end by nearly exhausting their families and friends.

The Care of the Patient, Francis Peabody, MD  JAMA 1927
Is this a Mast cell activation disorder (MCAD)?

My skin gets itchy and my asthma acts up every change of season.

Even if seafood is cooked in another room, Jamie gets a headache and her throat starts to close.

My sister breaks out in hives and feels faint if she jumps out of the pool.

With some foods, Katie becomes red in the face and has to run to the bathroom.

During ragweed season, my son gets stuffy. He also cannot eat fresh melons and bananas.

All my tests were normal but I get bloated, “gassy” and my joints hurt if I eat bread.
The diagnosis of Mast Cell Activation syndrome (MCAS) should be considered, when

(1) symptoms are recurrent (keep coming and going);

(2) laboratory tests detect an increase in mediators (chemical messengers) released by mast cells or find atypical, clustered mast cells in tissue biopsies from affected organs (skin, gut, bone marrow);

(3) the signs of symptoms of these reactions get better with treatments that block mast cell activation or the action of chemicals that get released by activated mast cells.

Valent, 2013
Living with Mast Cell Activation Syndrome

TEAM WORK!
Got MCAS?

The human race has come to dominate its environment so completely that any analysis of the increase or appearance of a disease has to take changes in our lifestyle into account. In the case of allergic disease changes in our environment, diet, water quality, and personal behavior over the last 150 years have played a dominant role in the specificity of these diseases, as well as in prevalence and severity.

Platts Mills, J Allergy Clin Immunol, 2017
To help navigate a new path through the maze of specialists, testing and treatments, here is a guide to Mast Cell Activation Disorders.

- New Set of Questions
- Suggested Tests
- Recommended treatment plans

✓ Coordinated Care between you, Your Primary Care Provider and Team of Medical Specialists
To Feel and Live Better - S.T.E.P. Up to Your Next Check Up!

✓ Screen
  ▶ Symptoms?
  ▶ Risk Factors?
  ▶ Previous treatments?

✓ Tests -
  ▶ MCAD
  ▶ MCAD co-morbid illnesses

✓ Educate yourself
  ▶ Triggers
  ▶ Recognition of MCAS symptoms

✓ Plan
Practitioner-Patient Partnership Guidelines ->
Mast Cell Activation Syndrome (MCAS) Control

- Prevent chronic and disabling symptoms
- Maintain normal function
- Provide optimal pharmacotherapy
- Maintain Normal Activity Levels
- Prevent Recurrent Exacerbations and Minimize the need for Emergency Department visits & hospitalizations
- Meet patients’ and families’ expectations with asthma care
When symptoms are recurrent, are accompanied by an increase in mast cell-derived mediators in biological fluids, and are responsive to treatment with mast cell-stabilizing or mediator-targeting drugs, the diagnosis of mast cell activation syndrome (MCAS) is appropriate.
Proposed Diagnostic Criteria: Mast Cell Activation Disorders

(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

(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+)
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.
Measuring Mast Cell Activation Markers, Inflammatory Mediators

Immediate Release
Granule contents:
Histamine, TNF-α, Proteases, Heparin

Over Minutes
Lipid mediators:
Prostaglandins Leukotrienes

Over Hours
Cytokine production:
IL-4, IL-6, IL-13

Urine
PGD2, 11-beta PGF2

Serum Tryptase

Serum, Urine Histamine

Pathology-spindle MC, MC aggregates

CD2, CD25 Expression
(3) Response to Treatment:
Targeting MC/MC Inflammatory Mediators

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

**Over Minutes**
- Wheezing, Bronchoconstriction

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

**Leukotriene Blockade**

**Corticosteroids**
**MC stabilizers**

**Traditional Chinese Medicine**
- Herbal Medicine
- Acupuncture

**Anti-IGE mAb**
Brain
Sense of uneasiness,
Angst/Anxiety
Headache, Dizziness
Confusion, Tunnel Vision

Airway Reactions (ENT/Lungs)
Throat tightening, Throat Swelling
Nasal congestion, Rhinorrhea
Wheezing, Dyspnea, Chest Tightness

Gastrointestinal tract
Nausea, Cramping
Abdominal Pain
Vomiting, Diarrhea

Heart, Blood Pressure
Fainting, Chest Pain
Fast Heart Rate,
Palpitations (pounding)
Weak pulse, Dizziness

Genito-Urinary tract
Uterine
Cramping
Swelling - labia

Pain: Joint, Muscle, Nerve

Skin
Hives (Urticaria), Itch
Flushing, Swelling
(Angioedema)
Roadblock #1
Delay in diagnosis of MCAD

(Mast Cell) disorders now cause problems of increased complexity and commonly involves several organ systems, so patients are often referred to a succession of different specialists, resulting only in confusion.

Allergy: the unmet need,
Royal College of Physicians, 2006
Roadblock #2
Delay in diagnosis of MCAD

- Few commercial tests available to detect MCA
- Not all mediators are MC specific (only tryptase)
- Failure to inform pathologists to stain for mast cells (anti-CD117 or anti-tryptase Antibodies)
- Not enough data on number or morphology of mast cells = worrisome for MCAD?
While the cause(s) of MCAS isn't clear...

"we have some clues that it might be something to do with the signaling that goes on at the mast cell surface."

- Hamilton, Reuters - Brigham and Women's Hospital, Boston, 2011
Not all Sensor triggered MC signaling is the same!
Roadblock #3:
Delay in diagnosis of MCAD
Mast Cell Suppression -> Symptoms -
No Better or Worse with Histamine Blockers??
Something wrong with the medications? Fillers, preservatives

**ACTIVE INGREDIENTS**
- Diphenhydramine
- Phenylephrine

**INACTIVE INGREDIENTS**
- Anhydrous chloric acid, Anhydrous trisodium Citrate, Carboxymethylcellulose, Edetate disodium, FD&C Blue #1, FD&C Red #40, “flavors”, glycerin, propyl gallate, propylene glycol, purified water, sodium benzoate, sorbitol, sucralose
(2) Are signs and symptoms of MC activation (MCA) an early warning signs of another disorder?
Mast Cell Activation Disorders

Or is it?

IT'S JUST "ALLERGIES"

Or is it?
Lessons from Urticaria

Chronic Urticaria (CU) Care:

- IgE-mediated reactions from foods, drugs, or other allergens
- Autoimmune urticaria: thyroid autoantibodies and IgE receptor autoantibodies

- Chronic infections: viral infections- hepatitis B and C, EBV, herpes simplex virus; Helicobacter pylori infections; and helminthic parasitic infections
- Antibody and Complement component deficiencies
- Serum sickness or other immune-complex mediated processes
- Autoimmune/Connective tissue diseases, systemic lupus erythematosus and rheumatoid arthritis
- Thyroid disease (both hypothyroidism and hyperthyroidism)
- Neoplasms (particularly lymphoreticular malignancy and lymphoproliferative disorders)

Histamine Blockers
Leukotriene Blockers
Cromones
Mast Cell activation (MCA) can be driven by other co-morbid illnesses: MCAD/MCAS Endotypes

- Allergic (IGE mediated) Disorders
- MC activation associated with chronic inflammatory/neoplastic disorders
  - Autoimmune Disorders
    - Chronic Autoimmune Urticaria
    - Rheumatology syndromes
  - Autoimmune Neuropathies
  - Immune deficiency Syndromes
- Physical Urticarias

Hypertryptasemia

Disorders associated with mast cell activation

Idiopathic Anaphylaxis

Mastcytosis Monoclonal MCAS

Clonal mast cell disorders
#1 Got MCAS?
If so, which form?

#2 Got EDS?
If so, which form?
Some food (wheat/gluten, peanuts, eggs, nuts and shellfish, milk*, egg*, soy*)

Medications

Airborne Allergens

Insect stings or bites

Autoimmune Disorders

Infections

Physical stimuli, such as pressure, cold, heat, exercise or sun exposure

Allergen testing

Rheumatology Panel
ANA, RF, ANCA, Thyroid Abs Neuonal Abs PIDD evaluation

PIDD evaluation
Primary Immune Deficiency Disorder

EDS Screen? Neuropathy?
Ten warning signs of primary immunodeficiency: a new paradigm is needed for the 21st century

Peter Arkwright & Andrew R. Gennery

The 10 warning signs of primary immunodeficiency are being promoted as a screening tool for use by both the general public and physicians.

A recent study, however, shows that except for family history, need for intravenous antibiotics and failure to thrive, the 10 warning signs are not a useful screen of primary immunodeficiency diseases (PIDs).

The 10 warning signs do not take into account the fact that PIDs now include diseases that present with

- sporadic infections,
- autoimmunity,
- autoinflammation, and
- malignancy.
New Paradox: MCAS and Primary Immune Deficiency (PID)

Mast Cell Activation Syndrome In The Setting Of Idiopathic CD4 Lymphopenia
Roizen, Peruffo & Maitland, AAAAI 2018

Annual recurrent infections among patients with MCA symptoms

Mast Cell Activation as a Presentation of Primary Immunodeficiencies
Roizen & Maitland, AAAAI 2018
Treatment of MCAS: Targeting the co-morbid disorders driving MC Activation

**Allergens**
- Avoidance measures (Diet, Environment)
- Medications: histamine blockade
- Desensitization (Immunotherapy)
- Omalizumab
- Anti-interleukin mAb

**Infections**
- Infection vs exposure/sensitization
- Hepatitis, Lyme, Borrellia, EBV, HSV

**Primary Immune Deficiency**
- Prophylactic Antibiotics
- Immune Globulin

**Autoimmune Disorders**
- Anti-inflammatory Agents
- Immune Globulin
When telling your story do remember to write down those nuisance, “molehill” signs and symptoms.

Is that “mole hill” of symptom (hives, bloating, headache) an early sign of a mountain of health troubles?

Mountains out of Mole Hills
I frequently meet patients who are so overwhelmed by the fatigue, headaches or gastrointestinal distress, that he or she did not recall the large local reactions to insect bites, failed to take notice of the itch that is worse at night, or the trouble breathing when climbing stairs. These are all clues to reach a better working diagnosis!
All these individual symptoms may seem like a mole hill, rather than a mountain.

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But if the symptoms keep re-occurring, these molehills maybe a mountain of other or impending health problems.

When recalling your mountain of MCAD symptoms, do not forget the Molehills!
Stress Reduction & Regain Tolerance

I now believe that the ultimate power lies with the tissues. When healthy, tissues induce tolerance. When distressed, [the tissue] stimulates immunity, and (continuing down this path) they may also determine the effector class of a response.

Steps to feeling better

- Screen
- Testing
- Education
- Prevention

So that you are eating, sleeping, playing, working, with signs and symptoms of Mast Cell Activation Syndrome under control.
Gratitude!

- Patients and their families
- Colleagues
- Chiari Sryngomyelia Foundation
- Ehlers Danlos Society
- The Mastocytosis Society