Ehlers-Danlos Syndrome and its Fellow Traveler, Mast Cell Activation Syndrome

ANNE MAITLAND, M.D., PH.D.
ASST. PROFESSOR, DEPT. OF MEDICINE – CLINICAL IMMUNOLOGY DIVISION
MEDICAL DIRECTOR, COMPREHENSIVE ALLERGY & ASTHMA CARE, PLLC
Dr. Ehlers and Dr. Danlos described a distinct order including lax joints, hyper-extensible, skin and bruising.

400 B.C.: Hippocrates’ Airs, Waters and Places

1657: Dr Job Janszoon van Meekeren’s case history of George Albes, a boy with hyperextensible skin

1892: Dr A N Chernogubov’s detailed association between hypermobile joints and skin findings

1901: Dr Edvard Ehlers’ case history describing a distinct disorder including lax joints, hyperextensible skin, and bruising

1908: Dr Henri-Alexandre Danlos’ case history describing a disorder much like that described by Ehlers


1998: Dr Peter Beighton et al’s publication of the Villefranche nosology classifying Ehlers-Danlos Syndromes
But...

What is Ehlers-Danlos Syndrome (EDS)?

Ehlers-Danlos Syndrome is a heritable disorder of connective tissue (HDCT)

Heritable Disorders of Connective Tissue (HDCT) are passed from parent to child

HDCTs affect the "cellular glue" holding tissues of the body together
  - change the look, growth, or function of tissues such as skin, bones, joints, heart, blood vessels, and numerous other organ systems

There are multiple types of HDCT:
  - EDS
  - Marfan Syndrome, Osteogenesis Imperfecta, Loeys-Dietz Syndrome, Stickler Syndrome, Alport Syndrome, Beal's Syndrome, Epidermolysis Bullosa, and many, many more.
The Structure of Connective Tissue

Cells
- Fibroblasts, adipocytes, RBCs, WBCs (Mast Cells), chondroblasts, osteoblasts

Extra-Cellular Matrix
- Ground Substance
- Fibers
- Microfibrils

- Fat Cell
- Melanocyte
- Reticular Fibers
- Elastic Fibers
- Collagen Fibers
- Capillary Blood Vessel
- Macrophage
Factors that Influence the Structure of Connective Tissue

- Fat Cell
- Melanocyte
- Reticular Fibers
- Elastic Fibers
- Collagen Fibers
- Macrophage
- Mast Cell
- Capillary Blood Vessel

- genetic factors
- environmental triggers
- immune dysregulation
Ehlers-Danlos syndrome (EDS) is a heterogeneous group of inherited connective tissue disorders

<table>
<thead>
<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>Skin extensibility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jt hypermobility</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>

- Group of inherited connective tissue disorders caused by defect in collagen synthesis
  - structural proteins or
  - proteins/enzymes involved with collagen biogenesis

- EDS subtypes can be diagnosed **clinically** or genetically
Orthopedic features of hypermobility Ehlers Danlos Syndrome

![Images of various orthopedic features](image-url)
So why is an Allergy/Immunology specialist talking about EDS?
“many neurologists and cardiologists specializing in [EDS] and POTS have anecdotally observed that the use of antihistamines and other mast cell directed therapies offers benefit to manage symptoms in some patients”

... patients often describes “allergic-like” reactions to a variety of stimuli, including food, odors and medications. Thus, the allergy/immunology specialists are increasingly requested to evaluate such patients.”

Doherty & White, Autonomic Neuroscience, 2018
Meet Sean. He has been coping with hives, food sensitivities, anaphylaxis, asthma and flushing since birth...

September 2012

To whom It may concern:

I am a mother of a young child suffering from ... Mast Cell Activation Syndrome.

My son’s diet consists of 6 safe foods. In his 4 years of life, he’s experienced six episodes of anaphylaxis. Our day-to-day living is a constant struggle between pain, fatigue and allergic reactions.

To date, he’s seen 10 allergists, 4 orthopedists, 4 gastroenterologists, 3 geneticists, 2 nutritionists, 2 rheumatologists, 2 endocrinologists, 2 physical therapists, a cardiologist, a neurologist, and a pulmonologist, all to no avail.

My son’s “complex case” often leaves doctors bewildered or in disbelief. Only recently have we stumbled upon a doctor who is open minded and dedicated to helping us find answers....

Tina T.
Lessons from Chronic Urticaria: Allergic and Nonallergic Triggers

- 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

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)

Autoimmune urticaria: thyroid autoantibodies and IgE receptor autoantibodies
No allergies, but still reacting!
Can EDS be the key to collagen disorders?
Dr. John B. Symes.....

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.

Hmmm...”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 dog breeds 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
Letter to the Editor

Atopy in Connective Tissue Disorders

An early observation of a possible relationship between connective tissue and mast cells.
One Gene Mutation Links Three Mysterious, Debilitating Diseases:

Hypertryptasemia, tryptase > 9 ng/ml
(personal communication with J. Milner, MD, PhD)

“On a good day, my shoulders, knees, and hips will dislocate two to five times apiece. The slightest bump into a table or door will bloom new bruises on my arms and legs or tear a gash in the thin skin on my hands. My blood pressure will plummet each time I stand, making me feel woozy, nauseated, and weak. I’ll have trouble focusing and remembering words. I’ll run my errands from underneath an umbrella to prevent an allergic reaction to the Sun.”

-Kate Horowitz, Mental Floss, October 2016
Our findings link germline duplication in TPSAB1 (the alpha-tryptase gene) with:

- Irritable bowel syndrome
- Cutaneous complaints
- Connective Tissue Abnormalities
- Dysautonomia

Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number.
EDS- Hypermobility Syndrome = a hereditary condition with predominant rheumatologic manifestations...

It is now emerging as a multi-systemic disorder with widespread manifestations...

Castori, Dermatology 2012
Inherited Connective Tissue Disorders and Mast Cell Activation Syndromes
Diagnostic Criteria: Mast Cell Activation Disorders

Rhinitis
- 7 patients (78%) had chronic rhinitis symptoms, nasal congestion, over the past month.
  - Majority with symptoms severe enough to interfere with sleep.

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

Symptoms that were controlled on anti-mediator therapy:
- Anti-histamine
- Mast cell stabilizer
- Leukotriene modifier
Diagnostic Criteria: Mast Cell Activation Disorders

**Asthma**

7 patients (78%) had a history of asthma.

- All patients with a history of asthma were treated with a rescue inhaled beta-agonist.
- 44% were on an inhaled corticosteroid, 78% were on a leukotriene modifier.

**Anaphylaxis**

Patients (78%) reported previous symptoms highly likely to be anaphylaxis based on clinical diagnostic criteria:

- acute onset of illness
- either spontaneous or after exposure to common MC triggers
- involving skin, mucosal tissue, hypotension, and respiratory and gastrointestinal symptoms.
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
## Results: MCAS-ish

<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></td>
<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>
</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>
MCAS-ish and EDS: Objective Data

9 patients were tested for objective evidence of mast cell activation, including:
- serum tryptase levels were normal
- Serum IGE < 20 kiu/ml (3-20)
- 24 hour urine histamine collections were unremarkable.

All Ehlers Danlos Syndrome patients appear to display non-IgE mediated allergic disease controlled by anti-mediator therapy and avoidance of triggers.

- Symptoms?
- Test Results?
- Better with treatments that target MC or MC mediators?
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
"MCAS-ish": Few or No Allergies, but Still Reacting

UNDERSTANDING
MAST CELL ACTIVATION (MCA)
and
MAST CELL ACTIVATION
SYNDROME (MCAS)
Our immune systems ... can be defined a priori as embodied expectations of injury and the corresponding programs of protection and repair.
In imperial times, the Great Wall of China was easily breached and was not in itself a very effective defense against resolute adversaries. Rather, it was a communication route and housed, far from the imperial centre, a string of lonely guards who quickly engaged invaders and slowed their progress, while alerting and beckoning more substantial back-up forces.

Mast Cell Orders

MAST CELL BIOLOGY 101
Mast Cell Development

Bone Marrow: Pluripotent CD34+ Progenitors
Blood Stream
SCF-Kit: *Homing to tissues
*Granule Production
*Local Survival
Homeostasis: Keeping the Peace

Like a police officer, who strives to serve and protect a neighborhood, “rookie” Mast Cells arrive and learn to meet the needs of local community of cells and tissue.

- Trained and prepared with different tools, each individual police officer must learn how to serve and protect his or her assigned, local neighborhood.
Mast Cell Activation/Orders: Border Patrol

- Fat Cell
- Lymphocyte
- Macrophage
- Capillary Blood Vessel
- Melanocyte
- Reticular Fibers
- Mast Cell
- Collagen Fibers
- Elastic Fibers
Depending on the nature and severity of the danger, the police officer will respond with a defined, regulated series of actions.
Armed with invariant sensors, Mast Cells are hardwired to recognize and then react with a defined set of chemical and physical responses, in order to contain “usual suspects”, pathogens and harmful substances.
Mast Cells act as the local Peace Keepers, maintaining homeostasis in the surrounding microenvironment.

And, through chemical mediators and receptors, will call for...

911... what’s your emergency?

Depending on the nature and severity of the danger, mast cells, will respond with a defined set of mediators, calling for appropriate help.

Mast Cell Recognizes This...

parasite

And, through chemical mediators and receptors, will call for...

virus

Code Blue

bacteria

Code Red

Insect sting

Code Orange

Vascular leakage -> Serum Proteins -> Swelling, Itch
Mast Cells?

Part of the innate immune system

Mature MCs are found in the tissue
Our Immune system: Border Patrol: Not just self or nonself, but safe vs. danger!
(1) Damage Alert: Endogenous, self alarm signals, indicating danger:

breakdown products of hyaluron (made when vessels are damaged).
mammalian DNA, RNA, heat shock proteins (Hsps), interferon α, interleukin-1beta, CD40-L

(2) Threat recognition & Response

pattern recognition receptors (PRRs)
membrane-bound Toll-like receptors (TLRs), Complement receptors, Immunoglobulin Receptors on MCs
Mast Cell Activation: Border Defense and Tissue Repair
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.
Mast Cell Activation Disorders (including MCAS)
Valent, Allergy 2013

- Symptoms?
- Better with treatments that target MC or MC mediators?
- Test Results?
MCAD can be... 

"the aberrant release of variable subsets of mast cell mediators"

- Histamine
- Leukotrienes
- Prostaglandins
- Tumor Necrosis Factor
- Interleukins
# Mast Cell Activation Disorders: Signs and Symptoms

**Mastocytosis**

(ESCRIBANO ET AL, JACI 124:514)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin Lesions</td>
<td>90%</td>
</tr>
<tr>
<td>Pruritis</td>
<td>82%</td>
</tr>
<tr>
<td>Flushing</td>
<td>56%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35%</td>
</tr>
<tr>
<td>Abdominal Cramping</td>
<td>30%</td>
</tr>
<tr>
<td>Neuropsychiatric Symptoms</td>
<td>23%</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>23%</td>
</tr>
<tr>
<td>Peptic Symptoms</td>
<td>20%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>18%</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>12%</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>8%</td>
</tr>
</tbody>
</table>

**Nonclonal Mast Cell Activation Disorders**

(HAMILTON, J ALLERGY CLIN IMMUNOL 128;147)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td>94%</td>
</tr>
<tr>
<td>Dermatographism</td>
<td>89%</td>
</tr>
<tr>
<td>Flushing</td>
<td>89%</td>
</tr>
<tr>
<td>Headache</td>
<td>83%</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>67%</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>23%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>67%</td>
</tr>
<tr>
<td>Rhinitis (Naso-ocular)</td>
<td>39%</td>
</tr>
<tr>
<td>Asthma</td>
<td>39%</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>17%</td>
</tr>
</tbody>
</table>
**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

**Genito-Urinary tract**
- Uterine Cramping
- Swelling -labia

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

**Pain: Joint, Muscle, Nerve**

**Skin**
- Hives (Urticaria), Itch
- Flushing, Swelling
- (Angioedema)
(2) 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

Pathology-
- spindled MC, MC aggregates

Serum, Urine Histamine

Serum Tryptase

Urine PGD2, 11-beta PGF2

CD2, CD25 Expression
MAST CELL (MC) 101

- MCs are found in most parts of the body and are well known for their role in allergic/anaphylactic reactions.

- MCs are now recognized to play a role in a number of inflammatory diseases in the skin, respiratory tract, joints, gastrointestinal tract, nervous system, and bladder.

- MCs contain > 500 secretory granules and can de novo synthesize and release mediators following stimulation, via degranulation or differential, piecemeal release.

- Arachidonic acid products, biogenic amines, chemotactic factors, cytokines, growth factors, neuropeptides, proteoglycans, and proteolytic enzymes.

Theoharides, & Bielory, Annals Allergy, Asthma & Immunology, 2003
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.

- Body Aches
- Bone Pain
- Premature Osteoporosis/Osteopenia

- Nasal Congestion, Nasal Itch, Shortness of Breath, Throat Swelling, Wheezing

- Burning Sensation/Pain, Urinary Frequency

- 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

- Malaise
- Weight Loss
- Weight Gain
- Fatigue

- Prostaglandins (PGs)
- Platelet Activating Factor (PAF)
- Interleukin-6
- Tumor Necrosis factor (TNF)
- Histamine

- Corticotropin Releasing Hormone (CRH)
- Tryptase
- Chymase
- Renin

- Histamine Interleukin-6
- Tumor Necrosis factor

- Prostaglandins
- PGs
- PAF
- Interleukin-6
- TNF
- Tryptase
- Serotonin
- Prostaglandins
(3) Response to Treatment:
Targeting MC/MC Inflammatory Mediators

- **Anti-IGE mAb**
- **Histamine Blockade**
  - Tricyclic Agents

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

**Over Minutes**
- Lipid mediators:
  - Prostaglandins
  - Leukotrienes

- Wheezing
- Bronchoconstriction

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

**Traditional Chinese Medicine (TCM)**
- Herbal Medicine
- Acupuncture

**Corticosteroids**
- MC stabilizers

**Leukotriene Blockade**

**Symptoms**
- Sneezing
- Nasal congestion
- Itchy, runny nose
- Watery eyes
Looking for Mast Cells?

Ask the pathologist:

MCs: CD117, anti-tryptase

MC activation markers: CD2, CD25, CD30

Expression

Under the Microscope:
A sign of mastocytosis: Mast cells, that are spindled shaped (no longer round) and are clustered.
What’s tickling the MCs?

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."

- Dr. Matthew J. Hamilton of Brigham and Women's Hospital, Boston, 2011
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

“l’ll do some tests rather than give you a guess.”

- Histamine
- Heparin
- Leukotrienes
- Chemokines
- Tumor Necrosis factor
- Cytokines
- Enzymes
- Chymase
- Tryptase
- Serotonin
- Nerve Growth Factor

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?
Mast Cell Suppression → Symptoms — No Better or Worse with Histamine Blockers??

MCAD/MCAS Treatment:
Targeting MCs or MC derived Inflammatory Mediators

- Corticosteroids
- MC stabilizers
- Cytokine Antagonists

Histamine Blockade
Tricyclic Agents

- Leukotriene Blockade
- Cyclooxygenase Inhibitors

Nutraceuticals
- DAO supplement
- Vitamin C
- Quercetin
- Stinging Nettle
- Butterbur

Traditional Chinese (TCM)
Herbal Medicine
Acupuncture

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

Over Minutes
Lipid mediators:
Prostaglandins
Leukotrienes

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

Theoharides et al, NEJM 2015; Engler et al, J Allergy Clin Immunol, 2009;

Roadblock #3:
Delay in diagnosis of MCAD
Not all Sensor triggered MC signaling is the same!
A CASE REPORT... Is it MCAS?

HER STORY...

Patient JK is a 41-year-old Caucasian Woman, now on disability.

JK has a history of chronic hives for over a year and comes for a second opinion on the cause of her hives, since the anti-histamines are no longer working to control her itchy rash.

She also has complained of episodes of bloating and has been treated for mood disorders and insomnia.

- Symptoms?
- Better with treatments that target MC or MC mediators?
- Test Results?
<table>
<thead>
<tr>
<th>TESTS</th>
<th>RESULT</th>
<th>FLAG</th>
<th>UNITS</th>
<th>REFERENCE INTERVAL</th>
<th>LAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC With Differential/Platelet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>6.7</td>
<td></td>
<td>x10E3/μL</td>
<td>4.0 - 10.5</td>
<td>01</td>
</tr>
<tr>
<td>RBC</td>
<td>4.01</td>
<td></td>
<td>x10E6/μL</td>
<td>3.77 - 5.28</td>
<td>01</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>12.2</td>
<td></td>
<td>g/dL</td>
<td>11.1 - 15.9</td>
<td>01</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>37.9</td>
<td></td>
<td>%</td>
<td>34.0 - 46.6</td>
<td>01</td>
</tr>
<tr>
<td>MCV</td>
<td>95</td>
<td></td>
<td>fL</td>
<td>79 - 97</td>
<td>01</td>
</tr>
<tr>
<td>MCH</td>
<td>30.4</td>
<td></td>
<td>pg</td>
<td>26.6 - 33.0</td>
<td>01</td>
</tr>
<tr>
<td>MCHC</td>
<td>32.2</td>
<td></td>
<td>g/dL</td>
<td>31.5 - 35.7</td>
<td>01</td>
</tr>
<tr>
<td>RDW</td>
<td>13.8</td>
<td></td>
<td>%</td>
<td>12.3 - 15.4</td>
<td>01</td>
</tr>
<tr>
<td>Platelets</td>
<td>293</td>
<td></td>
<td>x10E3/μL</td>
<td>140 - 415</td>
<td>01</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>70</td>
<td></td>
<td>%</td>
<td>40 - 74</td>
<td>01</td>
</tr>
<tr>
<td>Lymphs</td>
<td>23</td>
<td></td>
<td>%</td>
<td>14 - 46</td>
<td>01</td>
</tr>
<tr>
<td>Monocytes</td>
<td>6</td>
<td></td>
<td>%</td>
<td>4 - 13</td>
<td>01</td>
</tr>
<tr>
<td>Eos</td>
<td>1</td>
<td></td>
<td>%</td>
<td>0 - 7</td>
<td>01</td>
</tr>
<tr>
<td>Basos</td>
<td>0</td>
<td></td>
<td>%</td>
<td>0 - 3</td>
<td>01</td>
</tr>
<tr>
<td>Neutrophils (Absolute)</td>
<td>4.7</td>
<td></td>
<td>x10E3/μL</td>
<td>1.8 - 7.8</td>
<td>01</td>
</tr>
<tr>
<td>Lymphs (Absolute)</td>
<td>1.5</td>
<td></td>
<td>x10E3/μL</td>
<td>0.7 - 4.5</td>
<td>01</td>
</tr>
<tr>
<td>Monocytes (Absolute)</td>
<td>0.4</td>
<td></td>
<td>x10E3/μL</td>
<td>0.1 - 1.0</td>
<td>01</td>
</tr>
<tr>
<td>Eos (Absolute)</td>
<td>0.0</td>
<td></td>
<td>x10E3/μL</td>
<td>0.0 - 0.4</td>
<td>01</td>
</tr>
<tr>
<td>Baso (Absolute)</td>
<td>0.0</td>
<td></td>
<td>x10E3/μL</td>
<td>0.0 - 0.2</td>
<td>01</td>
</tr>
<tr>
<td>Immature Granulocytes</td>
<td>0</td>
<td></td>
<td>%</td>
<td>0 - 2</td>
<td>01</td>
</tr>
<tr>
<td>Immature Granul (Abs)</td>
<td>0.0</td>
<td></td>
<td>x10E3/μL</td>
<td>0.0 - 0.1</td>
<td>01</td>
</tr>
</tbody>
</table>

**Low Total Serum IGE**

**Tissue Inflammation??**

**Allergen-Specific IGE**

**Immunoglobulin E, Total**

| 9 | IU/mL | 0 - 100 | 01 |

**Complement, Total (CH50)**

| 63 | High | 22 - 60 | 01 |

**D001-IgE D pteronyssinus**

0.10 Abnormal kU/L

**D002-IgE D farinae Mite**

0.09 Abnormal kU/L

**E001-IgE Cat Hair/Dander**

2.23 Abnormal kU/L

**E002-IgE Dog Epithelia**

0.15 Abnormal kU/L

**G002-IgE Bermuda Grass**

0.13 Abnormal kU/L

**G008-IgE Bluegrass, Kentucky**

<0.08 kU/L

**G017-IgE Bahia Grass**

<0.08 kU/L

**I100-IgE Cockroach,American**

<0.08 kU/L

**M001-IgE Penicillium notatum**

0.11 Abnormal kU/L

**M002-IgE Cladosporium herbarum**

<0.08 kU/L

**M003-IgE Aspergillus fumigatus**

0.08 Abnormal kU/L

**M004-IgE Mucor racemosus**

<0.08 kU/L

**M006-IgE Alternaria tenuis**

<0.08 kU/L

**M010-IgE Stemphylium botryosum**

0.08 Abnormal kU/L

**T030-IgE Birch, White**

<0.08 kU/L

**T007-IgE Oak, White**

0.12 Abnormal kU/L

**T008-IgE Elm, American (White**
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Absent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial pain/pressure</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Facial congestion/fullness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Nasal obstruction/blockage</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Discolored or pus nasal discharge or post-nasal drip</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Decreased sense of smell</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Absent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Halitosis (bad breath)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue (tiredness)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Dental pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Ear pain/pressure/fullness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please estimate your medication usage as indicated below based on your care for the last 12 months:

**Nasal steroid sprays (Vasconase, Flonase, Nasacort, Rhinocort, Nasacort, etc)**

I currently use these medications [ ]
I used these medications for a total of [ ] weeks in the last 12 months

**Anti-histamines (Allegra, Claritin, Zyrtec, etc)**

I currently use these medications [ ]
I used these medications for a total of [ ] weeks in the last 12 months

**Antibiotics**

Number of courses in last 12 months [ ]
I spent a total of [ ] weeks on antibiotics in the last 12 months
My longest course of antibiotics lasted [ ] days

Please comment on how the nasal problem has affected your recent work and social status as listed below:

In the last 12 months, I missed a total of [ ] days of work/school due to nasal problems
In the last 12 months, I did not leave home for [ ] weeks due to my nasal problems
In the last 12 months, I visited a doctor or nurse [ ] times for my nasal problems
In the last 12 months, I had [ ] acute infections of my nose/sinuses
Many faces of Mast Cell Activation

**IgE receptor auto-antibodies**

**Tryptase >8 mcg/ml or higher, Hypertryptasemia?**

**Hypogammaglobulinemia**

---

#### Thyroid Panel With TSH

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>1.360</td>
<td>0.450 - 4.500 uIU/mL</td>
</tr>
<tr>
<td>Thyroxine (T4)</td>
<td>6.1</td>
<td>4.5 - 12.0 ug/dL</td>
</tr>
<tr>
<td>T3 Uptake</td>
<td>30</td>
<td>24 - 39 %</td>
</tr>
<tr>
<td>Free Thyroxine Index</td>
<td>1.8</td>
<td>1.2 - 4.9</td>
</tr>
</tbody>
</table>

#### Thyroid Antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid Peroxidase (TPO) Ab</td>
<td>11</td>
<td>0 - 34 IU/mL</td>
</tr>
<tr>
<td>Antithyroglobulin Ab</td>
<td>&lt;20</td>
<td>0 - 40 IU/mL</td>
</tr>
</tbody>
</table>

**Siemens (DPC) ICMA Methodology**

#### Chronic Urticaria cu index

- **cu index**: >50.0 High, <10.0

*The CU Index(R) test is the second generation Functional Anti-FcεRI test. Patients with a CU Index(R) greater than or equal to 10 have basophil reactive factors in their serum which supports an autoimmune basis for disease. This test was developed and its performance characteristics determined by Viracor-IBT Laboratories. It has not been cleared or approved by the FDA.*

#### Immunoglobulin E, Total

<table>
<thead>
<tr>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0 - 100 IU/mL</td>
</tr>
</tbody>
</table>

#### Tryptase

<table>
<thead>
<tr>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.3</td>
<td>2.2 - 13.2 ug/L</td>
</tr>
</tbody>
</table>

---

**Immunoglobulins A/G/M, Qn, Ser**

- **Immunoglobulin G, Qn, Serum**: 532 Low mg/dL 700 - 1600 mg/dL
- **Immunoglobulin A, Qn, Serum**: 85 mg/dL 70 - 400 mg/dL

**Effective September 10, 2012, the reference**

interval for Immunoglobulin A, Qn, Serum will be changing to:

- 0 - 11 months: 11 - 58
- 1 - 2 years: 20 - 101
- 3 - 6 years: 44 - 189
- 7 - 12 years: 62 - 236
- 13 - 17 years: 77 - 278
- 18 years and older: 91 - 414

#### Immunoglobulin M, Qn, Serum

<table>
<thead>
<tr>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>221</td>
<td>40 - 230 mg/dL</td>
</tr>
<tr>
<td>Antigen/Allergen</td>
<td>IgE Level</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>D001-IgE D pteronyssinus</td>
<td>0.10</td>
</tr>
<tr>
<td>D002-IgE D farinae Mite</td>
<td>0.09</td>
</tr>
<tr>
<td>E001-IgE Cat Hair/Dander</td>
<td>2.23</td>
</tr>
<tr>
<td>E002-IgE Dog Epithelia</td>
<td>0.15</td>
</tr>
<tr>
<td>G002-IgE Bermuda Grass</td>
<td>0.13</td>
</tr>
<tr>
<td>G008-IgE Bluegrass, Kentucky</td>
<td>&lt;0.08</td>
</tr>
<tr>
<td>G017-IgE Bahia Grass</td>
<td>&lt;0.08</td>
</tr>
<tr>
<td>I100-IgE Cockroach, American</td>
<td>&lt;0.08</td>
</tr>
<tr>
<td>M001-IgE Penicillium notatum</td>
<td>0.11</td>
</tr>
<tr>
<td>M002-IgE Cladosporium herbari</td>
<td>&lt;0.08</td>
</tr>
<tr>
<td>M003-IgE Aspergillus fumigatu</td>
<td>0.08</td>
</tr>
<tr>
<td>M004-IgE Mucor racemosus</td>
<td>&lt;0.08</td>
</tr>
<tr>
<td>M006-IgE Alternaria tenuis</td>
<td>&lt;0.08</td>
</tr>
<tr>
<td>M010-IgE Stemphyllum botryosu</td>
<td>0.08</td>
</tr>
<tr>
<td>T030-IgE Birch, White</td>
<td>&lt;0.08</td>
</tr>
<tr>
<td>T007-IgE Oak, White</td>
<td>0.12</td>
</tr>
<tr>
<td>T008-IgE Blm, American (White)</td>
<td></td>
</tr>
</tbody>
</table>

**JK’s CU:**

Many Triggers of MCA

Antigen triggers production of IgE antibodies.

Antigen bridges the gap between two antibody molecules, degranulation of the cell and release of histamine and other mediators.

Histamine increases the permeability and distension of blood capillaries.

IgE bind to the surface of mast cell or basophil.
Does JK have MCAS? Yes.

Symptoms?

Test Results?

Better with treatments that target MC or MC mediators?

hives, GI/ bloating neuro-psychiatric illness.

Elevated plasma histamine
Tryptase 8 ng/ml; 4.8 ng/ml
EGD- more than 40 MCs/HPF

Tried diphenhydramine, cetirizine, ranitidine, clemastine, cimetidine, loratadine
– “my life is H*** 24-7, 365 days of the year”
Lessons from Urticaria
Chronic Urticaria (CU) Care: Tailored Diagnostics and Therapeutics

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

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)

Autoimmune urticaria: thyroid autoantibodies and IgE receptor autoantibodies
A Mast Cell Activation Syndrome as a presenting sign of a Primary Immunodeficiency?
Living with Mast Cell Activation Syndrome

TEAM WORK!
Threat recognition & Response

Pattern recognition receptors (PRRs), membrane-bound Toll-like receptors (TLRs), Complement receptors, Immunoglobulin Receptors on MCs

Damage Alert: Endogenous, self alarm signals, indicating danger:

- Breakdown products of hyaluron (made when vessels are damaged).
- Mammalian DNA, RNA, heat shock proteins (Hsps), interferon α, interleukin-1beta, CD40-L
1) Symptoms?
2) Better with treatments that target MC or MC mediators?
3) Test Results?
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
Targeting the co-morbid disorders, which are driving MC activation.
Some food (wheat/gluten, peanuts, eggs, nuts and shellfish, milk*, egg*, soy*)
Medications
Airbone Allergens
Insect stings or bites
Autoimmune Disorders
Infections
Physical stimuli, such as pressure, cold, heat, exercise or sun exposure

Allergen testing
Celiac Panel
EGD/Colonoscopy

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

PIDD evaluation
Primary Immune Deficiency Disorder

EDS Screen? Neuropathy?
MCAD Endotypes “flavors of MCADs”

- Allergic (IGE mediated) Disorders
- MC activation associated with chronic inflammatory/neoplastic disorders
- Physical Urticarias
- Chronic Autoimmune Urticaria

Disorders associated with mast cell activation

Hypertryptasemia

Mastocytosis
Monoclonal
MCAS
**Allergens**
- Avoidance measures (Diet, Environment)
- Medications: histamine blockade
- Desensitization (Immunotherapy)
- Traditional Chinese Herbal Therapy
- Omalizumab
- Anti-interleukin mAb

**Autoimmune Disorders**
- Anti-inflammatory Agents
- Immune Globulin Supplement
- Traditional Chinese Herbal Therapy

**Connective Tissue Disorders**
Primary Immune Deficiency
  • Prophylactic Antibiotics
  • Immune Globulin Supplement

Autoimmune Disorders
  • Anti-inflammatory Agents
  • Immune Globulin Supplement
  • Traditional Chinese Herbal Therapy
Gratitude!

“We want someone who’s willing to take risks.”
Thank you!!

It takes a village!

Patients and their families
Chiari Syringomyelia Foundation
Ehlers Danlos Society
The Mastocytosis Society

Contact Information
Anne Maitland, MD, PhD
AsktheAllergist
DrAnneMaitland