Diagnostic and treatment challenges of patients with mast cell activation disorders

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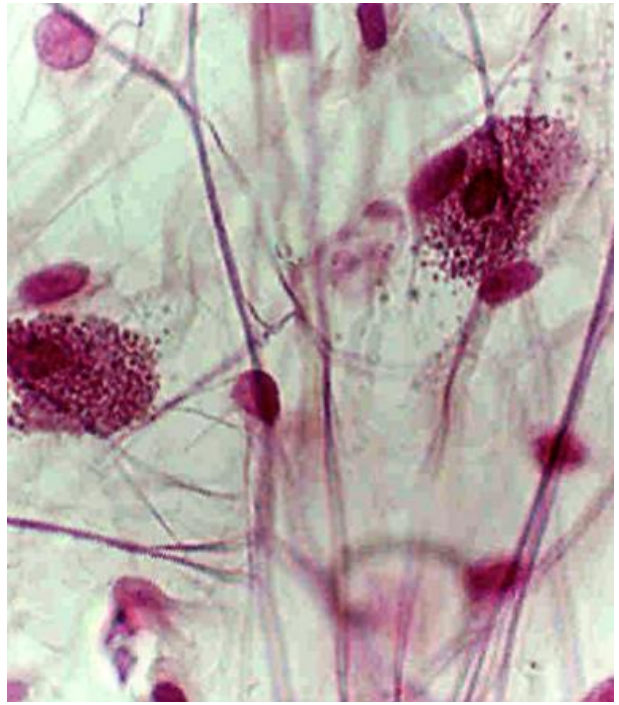
MEDICAL DIRECTOR, THREE PILLARS THERAPEUTICS AND

COMPREHENSIVE ALLERGY & ASTHMA CARE

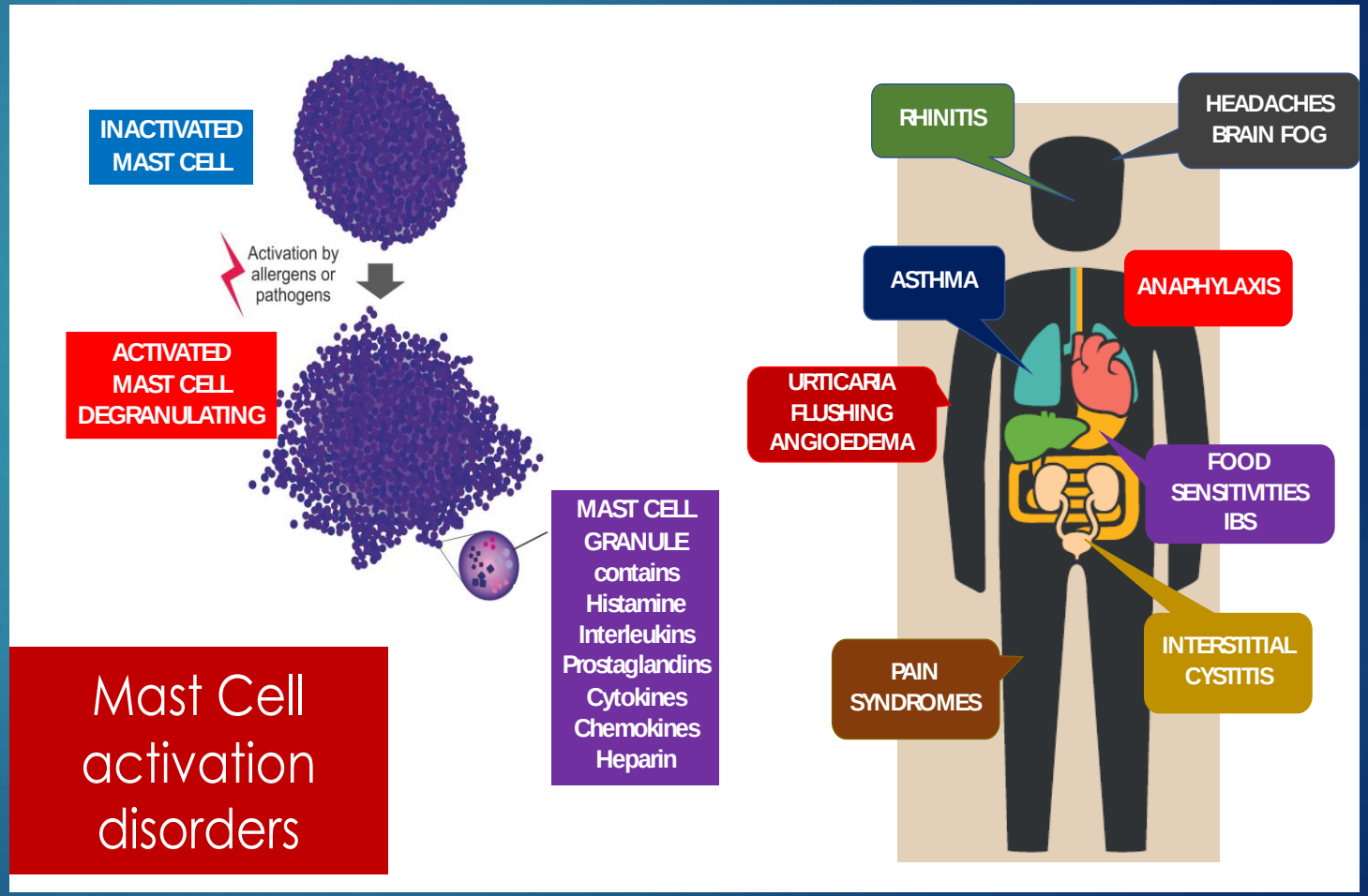


Conflict of Interest
Relevant financial relationships with commercial interests

NO DISCLOSURES

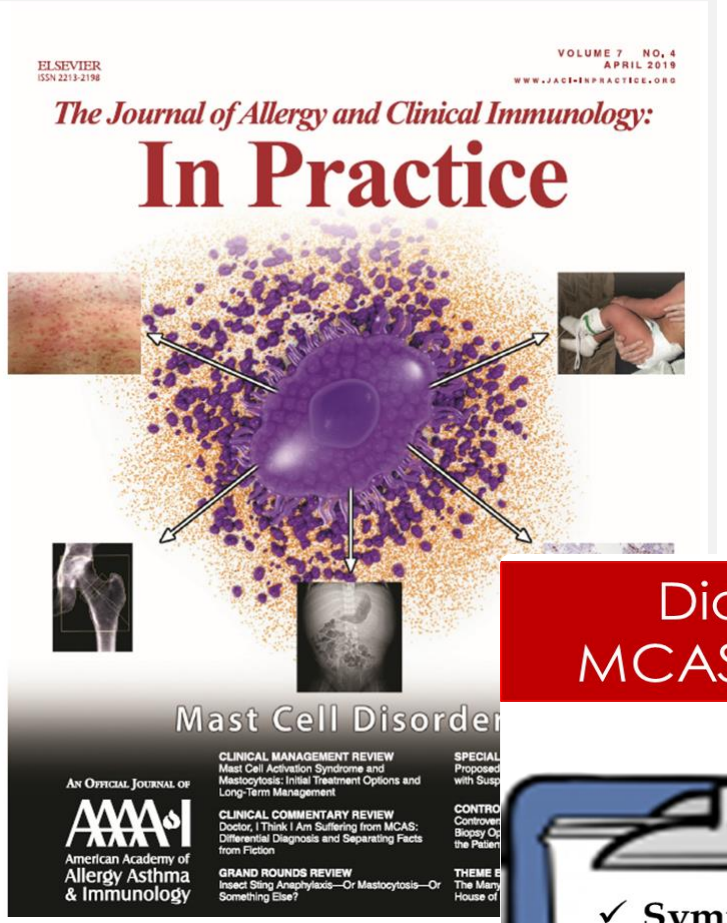
Objectives

- Recognition of mast cell derived mediators disease
- Understand diagnostic tools for mast cell activation disorders (MCAD), including mast cell activation syndrome (MCAS)
- Review of current treatment options for mast cell activation disorders



Consider the diagnosis of Mast Cell Activation (MCA) Syndrome

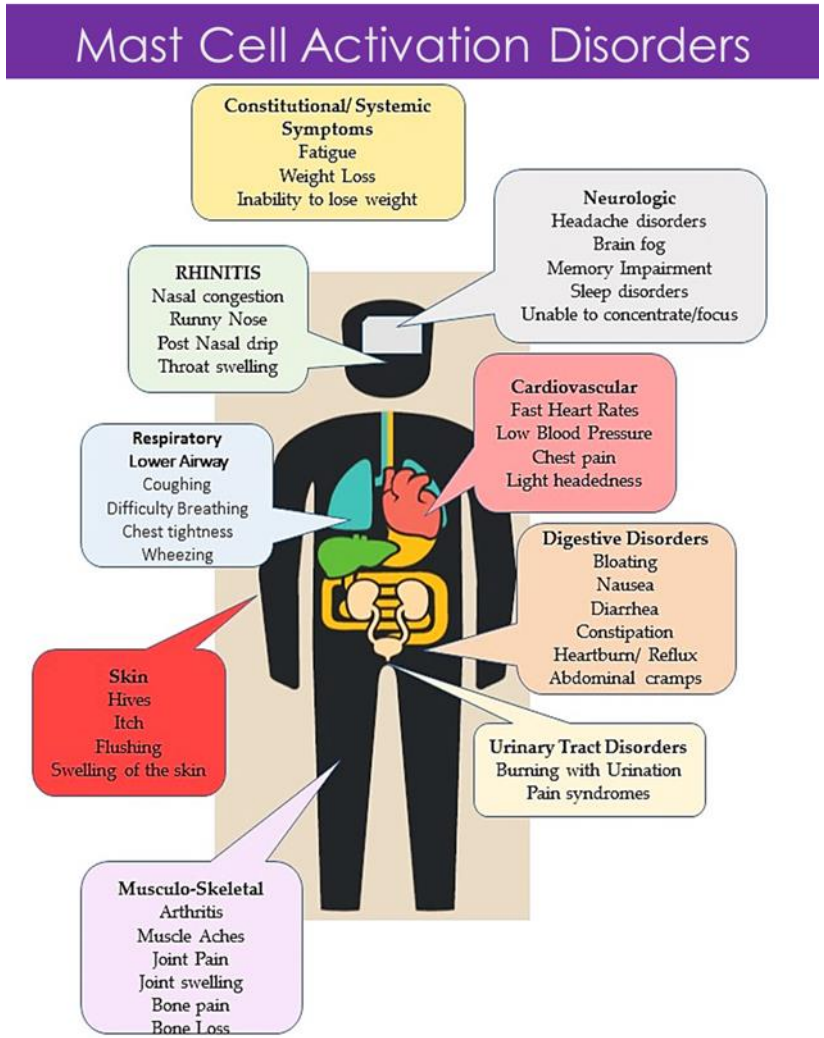
- RECURRENT TYPICAL SYMPTOMS
- LABORATORY ABNORMALITIES REFLECT MCA
- RESPONSE TO TREATMENT THAT TARGETS MC OR MC DERIVED MEDIATORS



Diagnosis: MCAS Checklist

- ✓ Symptoms?
- ✓ Better with treatments that target MC or MC mediators?
- ✓ Test Results?

MCA in 2 or more organ systems?



Mast cell activation syndrome: Proposed diagnostic criteria

Cem Akin, MD, PhD,[a]* Peter Valent, MD,[b] and Dean D. Metcalfe, MD[c] *Ann Arbor, Mich, Vienna, Austria, and Bethesda, Md*

Better with anti-MC/MC mediator medications?

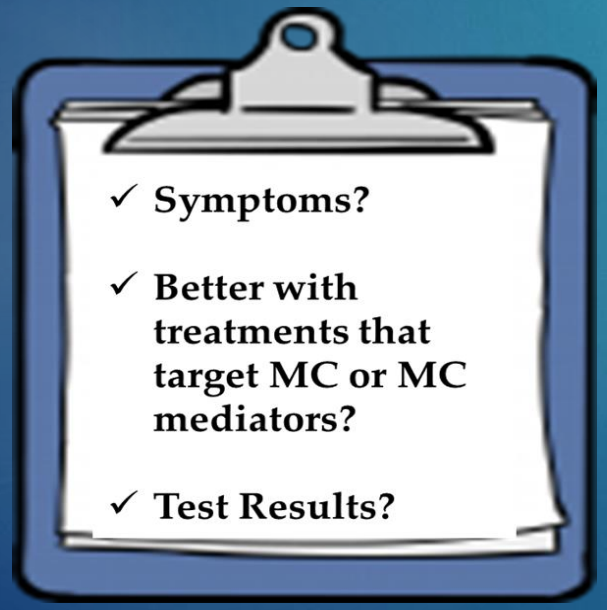
- Histamine Blockade
- Leukotriene Antagonists
- Cromones
- Omalizumab
- Ketotifen

MCA events associated w/ validated MCA markers

- Tryptase
- Urine Methylhistamine
- Urine Prostaglandin D2
- Urine 11- Beta Prostaglandin F2alpha
- C kit mutation- tissue, peripheral blood
- CD25+ MC in biopsies
- Clustered MC in biopsies

Delayed Diagnosis, leading to delayed tailored treatments, is common for patients with MCAD.

Diagnosis: MCAS Checklist



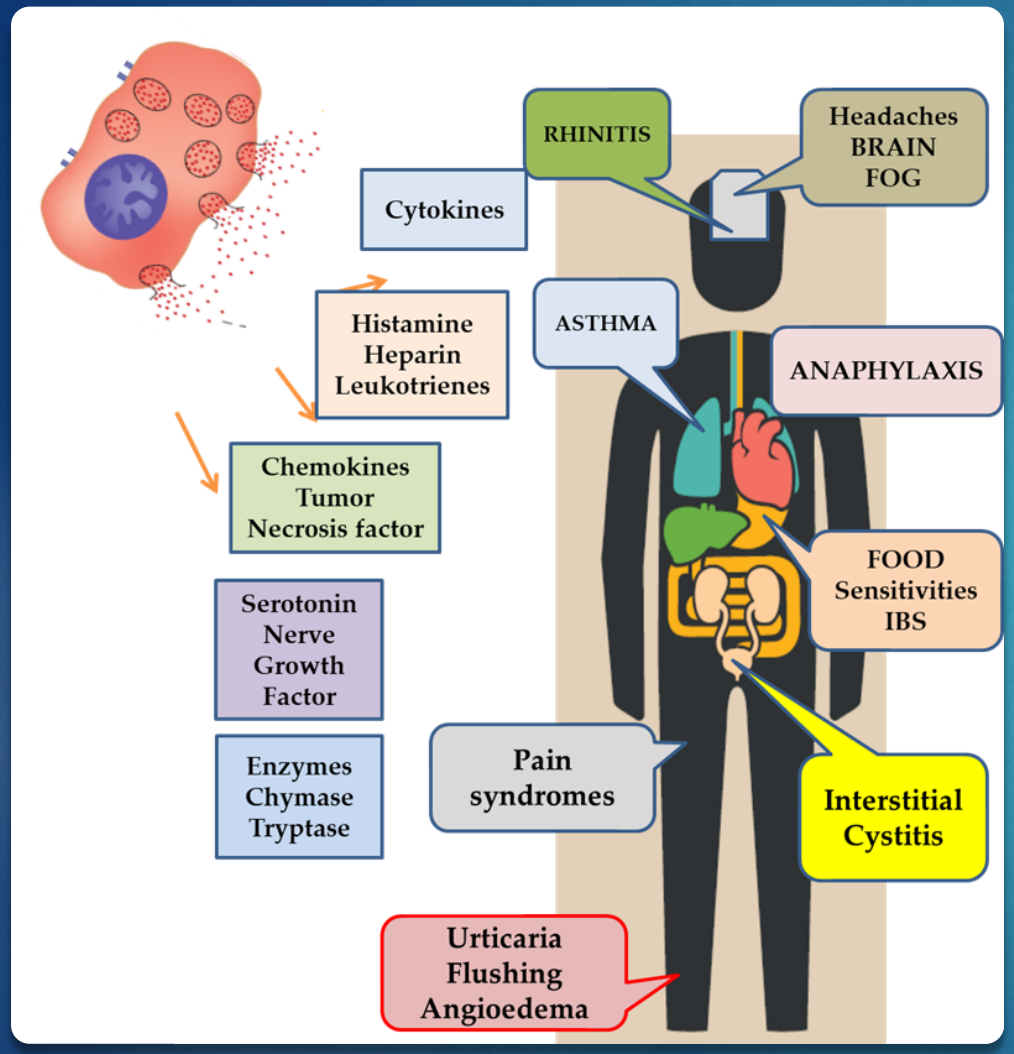
Ohio soccer player battles life-threatening reactions triggered by exercise

Caitlin McComish, 20, a former goalie for the University of Toledo, has cholinergic urticaria. A 'perfect storm' of factors, including heat and exercise, will make her throat and tongue swell. BY Victoria Taylor NEW YORK DAILY NEWS Friday, April 18, 2014, 3:50 PM

Rare disease makes woman allergic to everything, including her husband

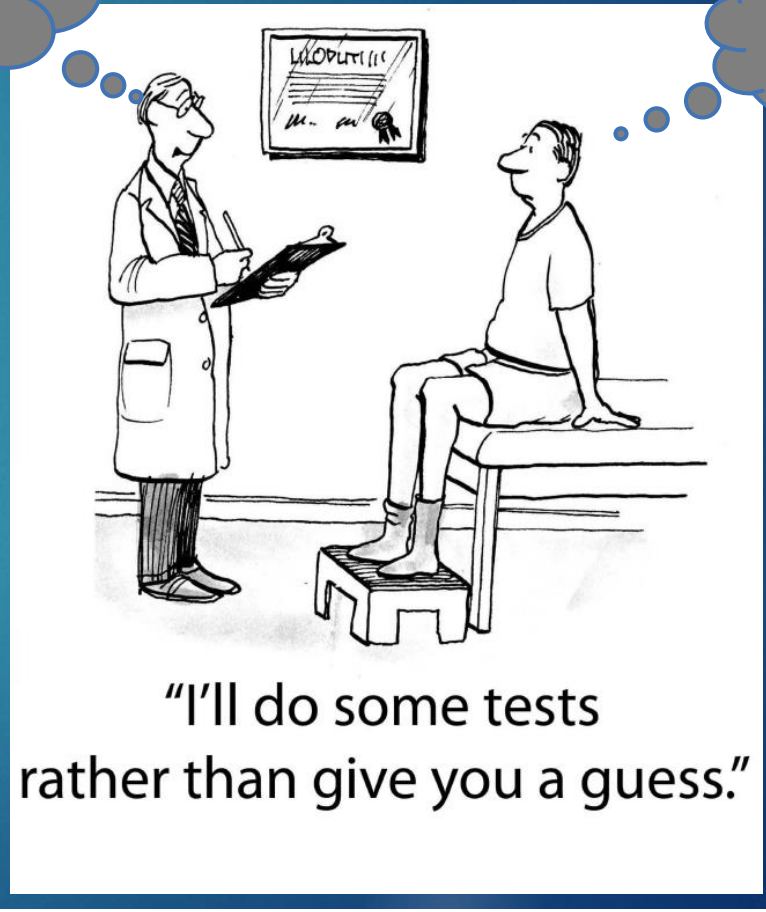
A young married couple is dealing with a rare disease that forces her to live in isolation from him and other people. by A. Pawlowski Source: TODAY / Feb.22.2017 / 2:07 PM EST / Updated Dec.27.2017 / 10:13 AM EST /

What's the hold up?



PCP delay

Patient Delay



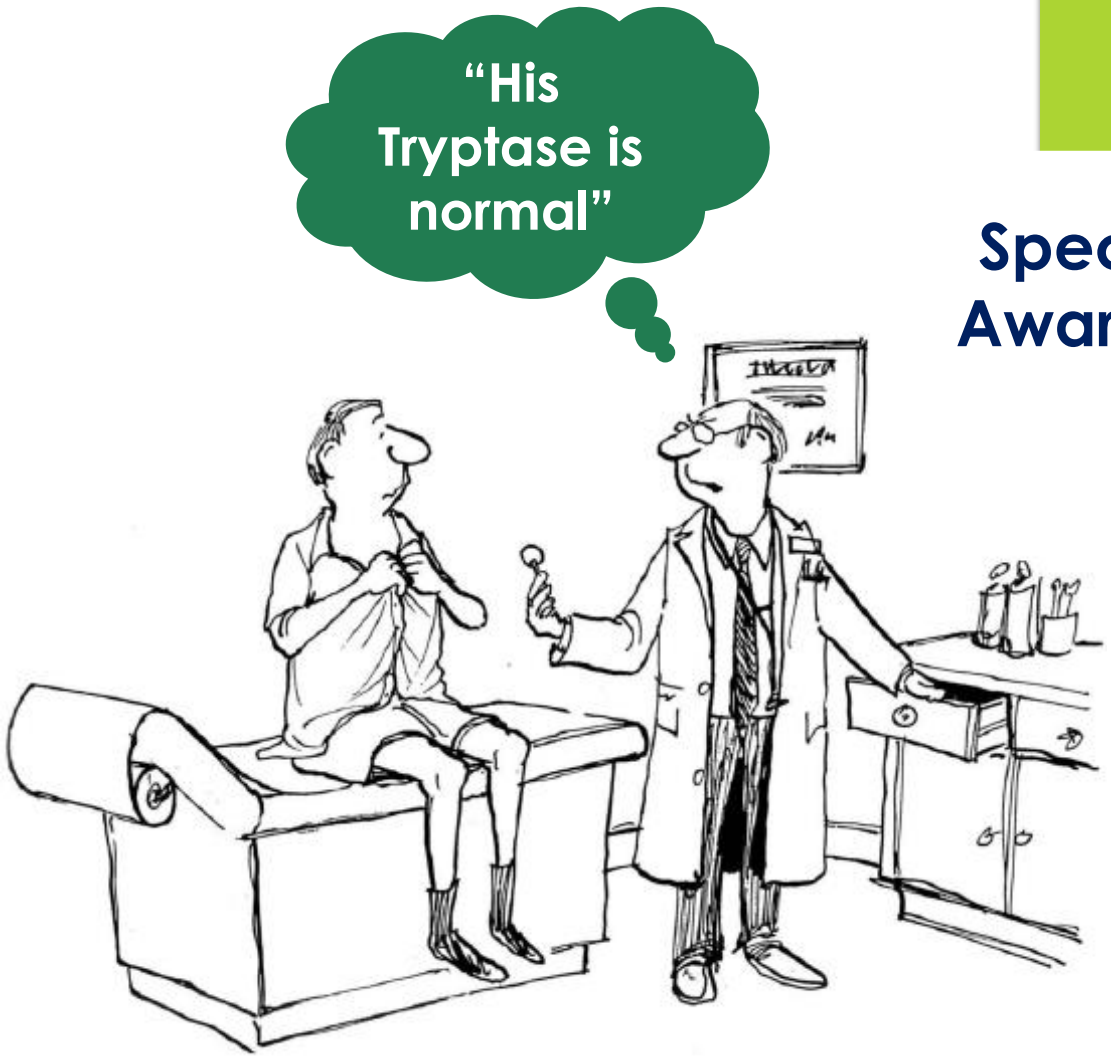
"I'll do some tests rather than give you a guess."

MCAD Delayed Diagnosis:

Specialists

- Lack of specialists in academic medical centers and communities = significant wait time
- Clinical manifestations of the multi-organ system disease
- " normal' test results

Specialist Awareness

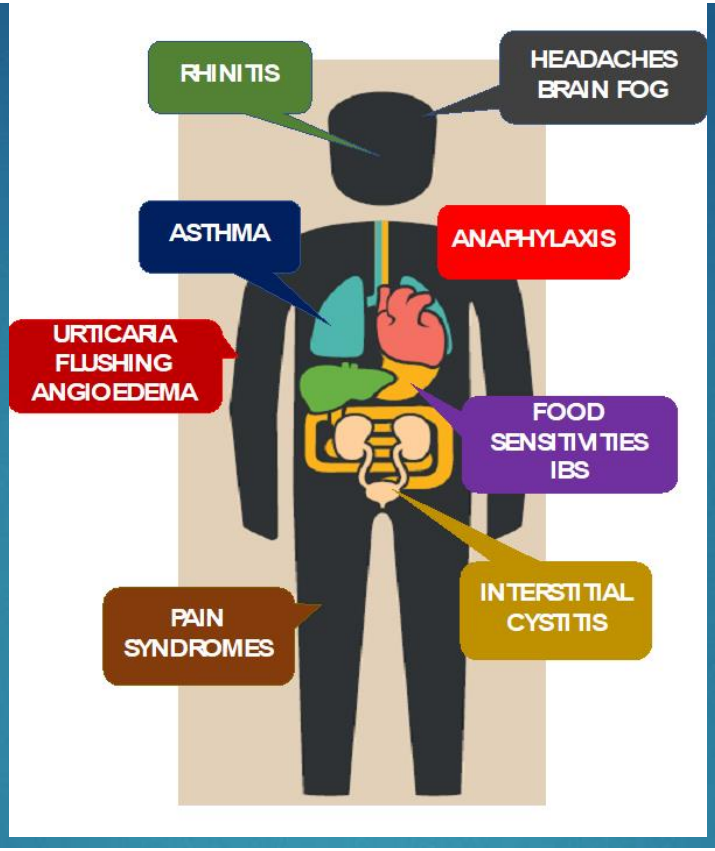


"You're fine.

Take a lollipop."

IgE and MCs have been so convincingly linked to the pathophysiology of anaphylaxis and other acute reactions that it can be difficult to think of them in other contexts

- Galli and Tsai, Nature Med, 2013



THE NEW YORK TIMES, THURSDAY, JANUARY 12, 1989

Scientists Find How Allergic Reaction Works

By HAROLD M. SCHMECK Jr.

Scientists have discovered the structure of a substance that is a key to allergic reactions, and they expect to use the knowledge soon in searching for new treatments for these widespread and varied forms of illness.

The substance being studied is the cell surface receptor to which anti-

substance to which the patient was allergic.

Most current treatment involves drugs that attempt to desensitize a person to a specific cause of an allergy.

'A Landmark Accomplishment'

"We believe this is a landmark accomplishment in allergy research,"

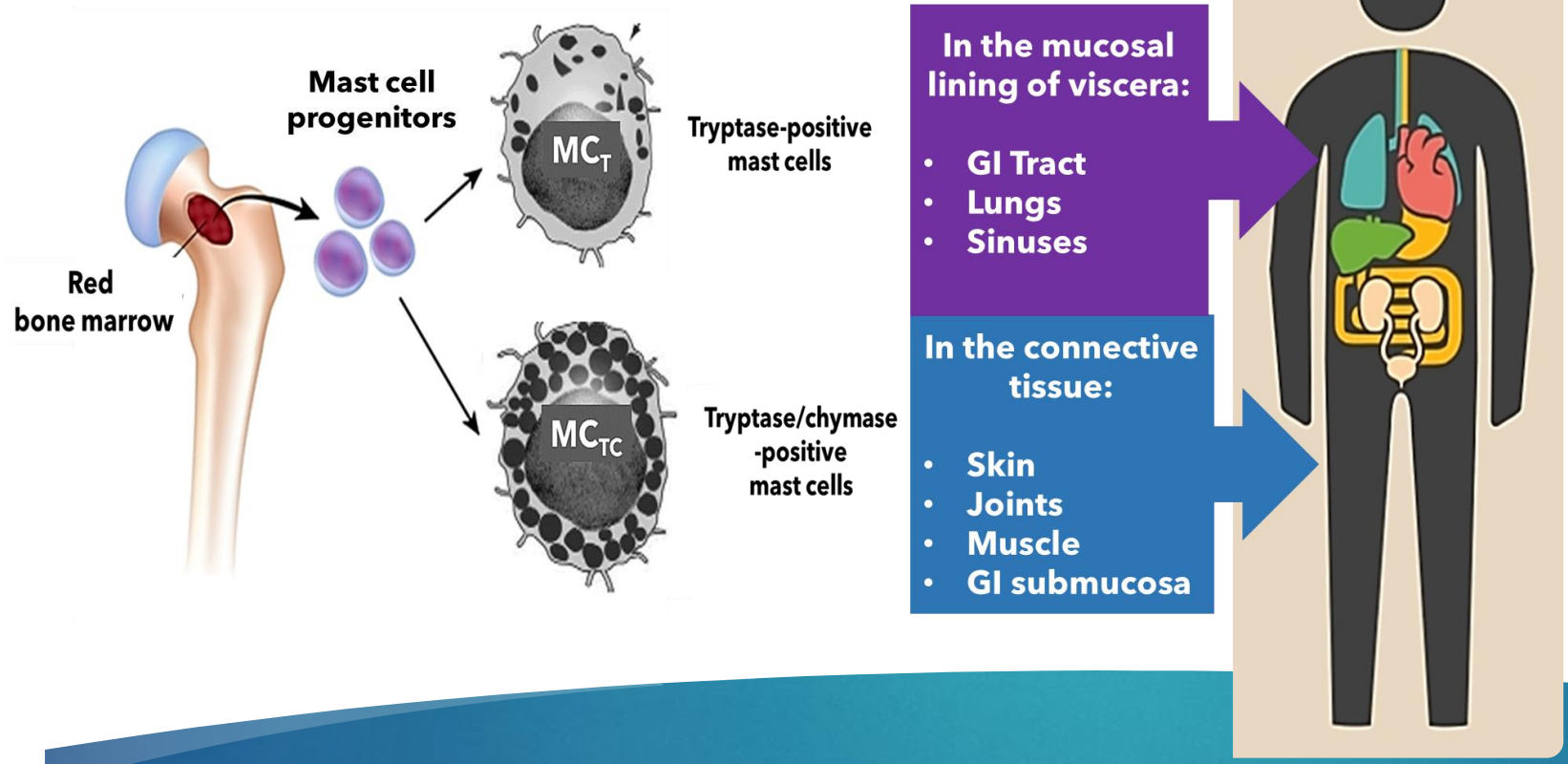
of three parts. Two parts were previously discovered, but were found to be inactive by themselves.

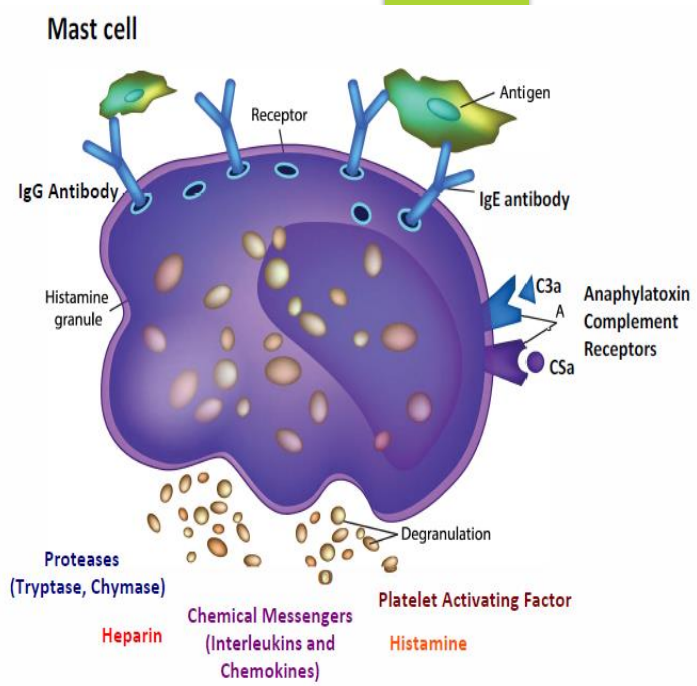
The Government scientists, led by Dr. Metzger and Dr. Jean-Pierre Kinet of the institute, identified the gene for the third component of the receptor and demonstrated that the three parts together functioned in cells. The re-

stance enters the body and is sought out by a particular class of antibodies called immunoglobulin E, or IgE. These attach to the foreign substance and also attach to receptors on immune defense cells called mast cells.

Cells Seem to Explode

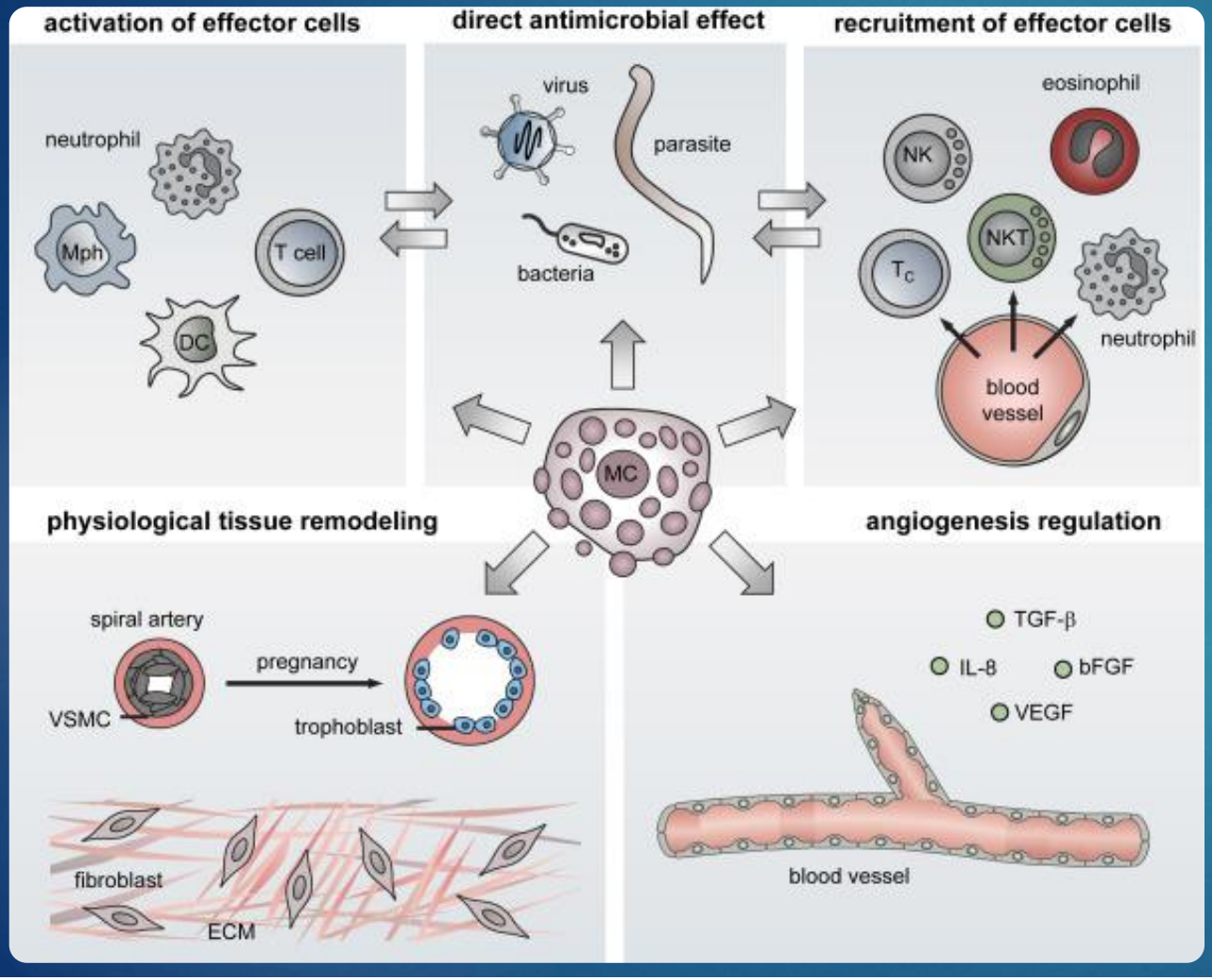
When the attachment is completed between the foreign substance, the antibodies and the receptors on the surface of the mast cells, the cells seem almost to explode. This reaction releases histamine and other substances that

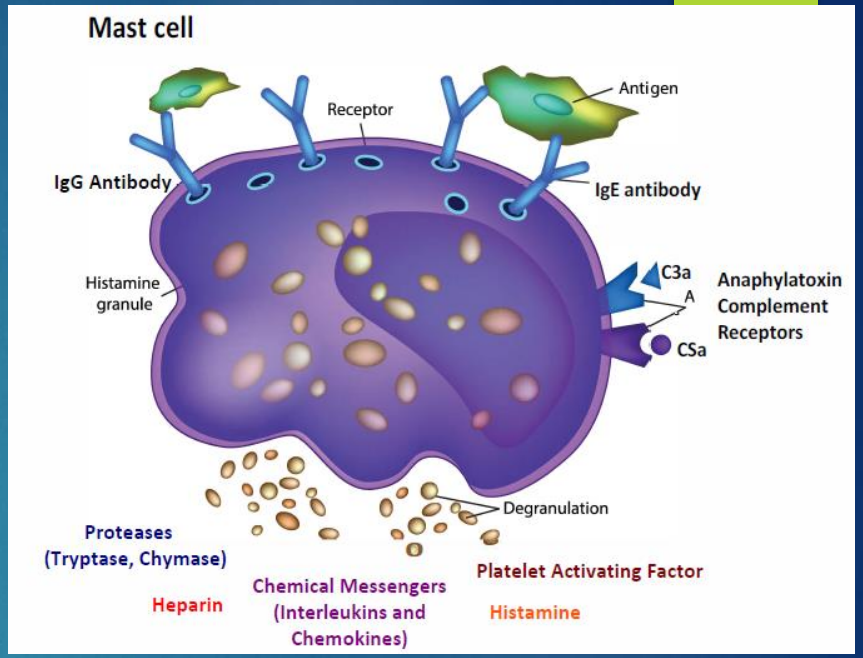




Mast Cell Activation: Beyond Allergies

MC Activation Orders





MCAD signs and symptoms

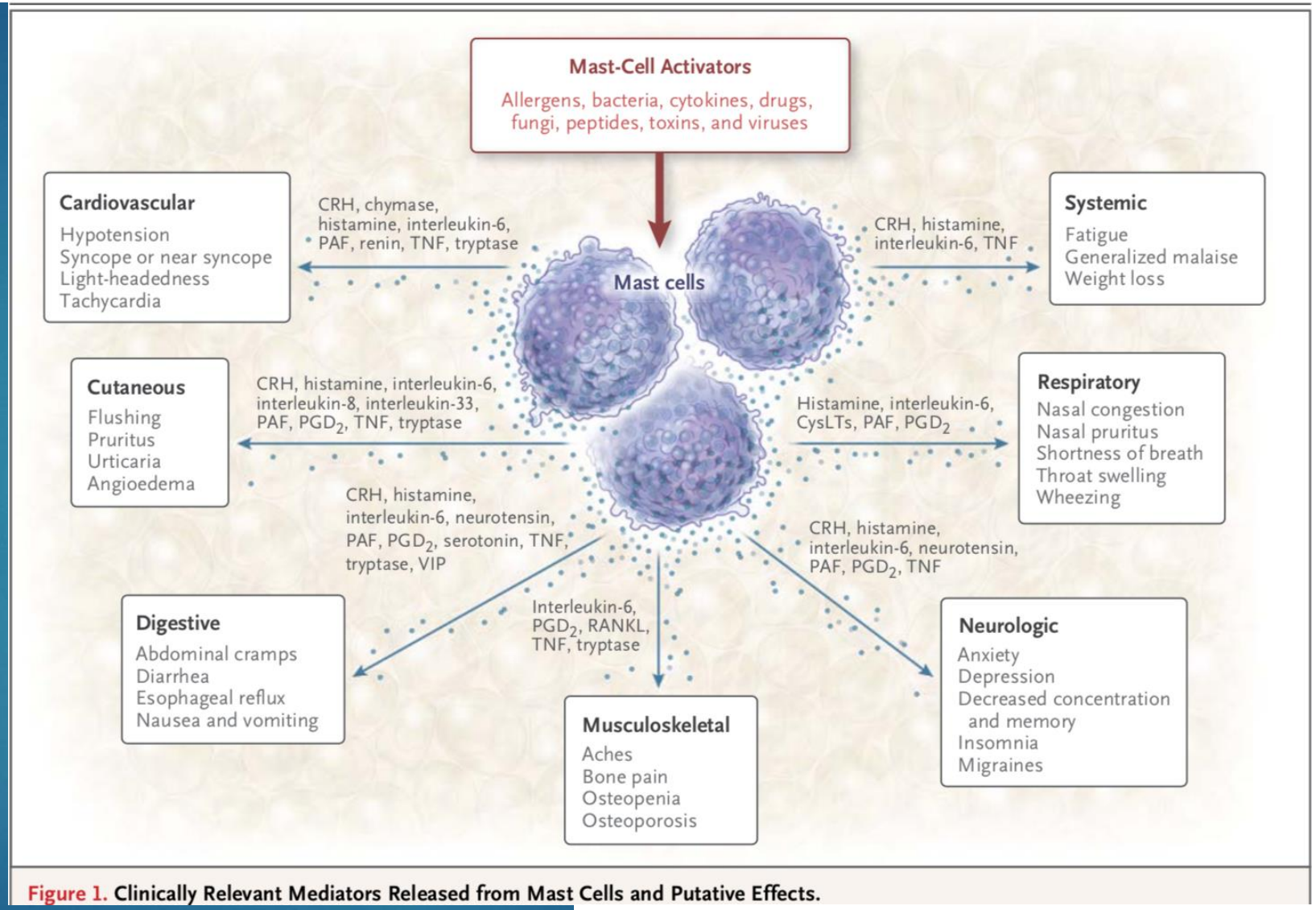
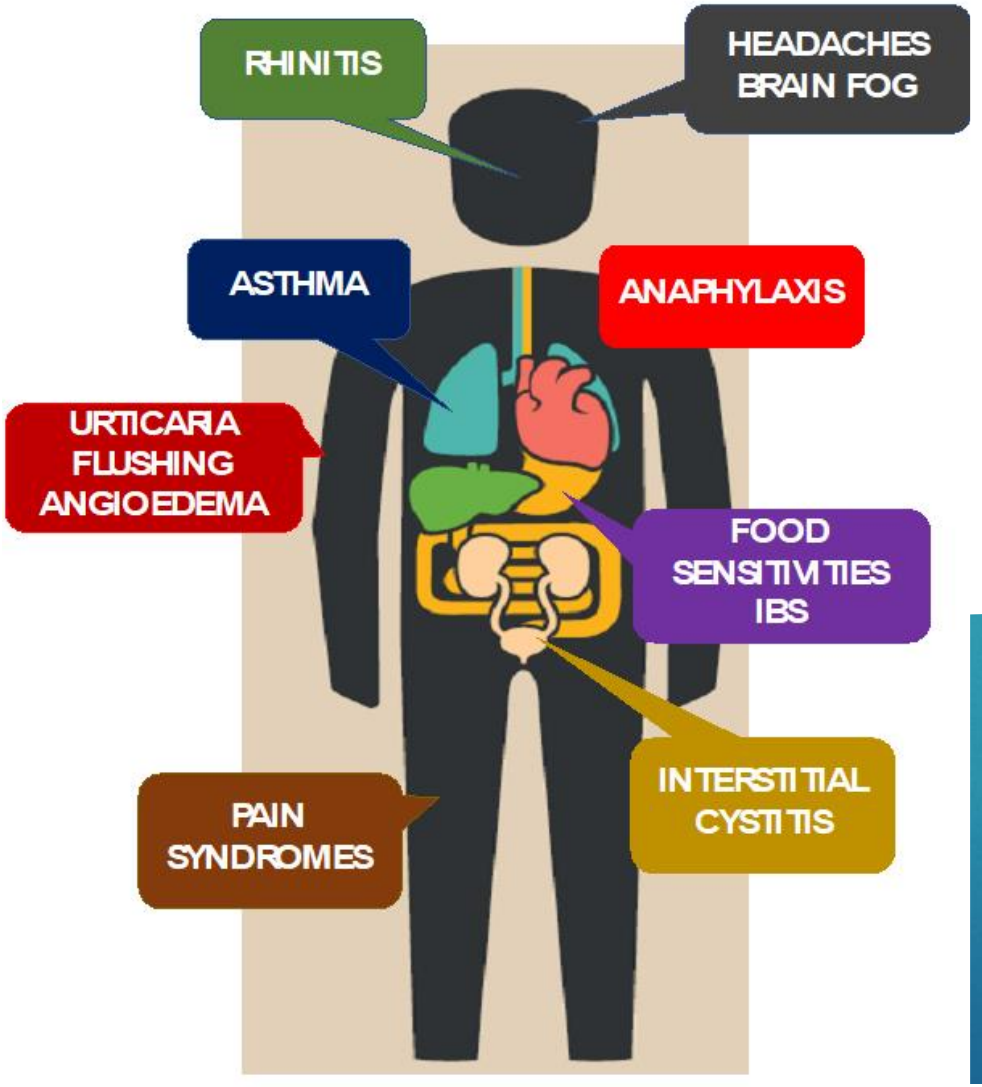


Figure 1. Clinically Relevant Mediators Released from Mast Cells and Putative Effects.

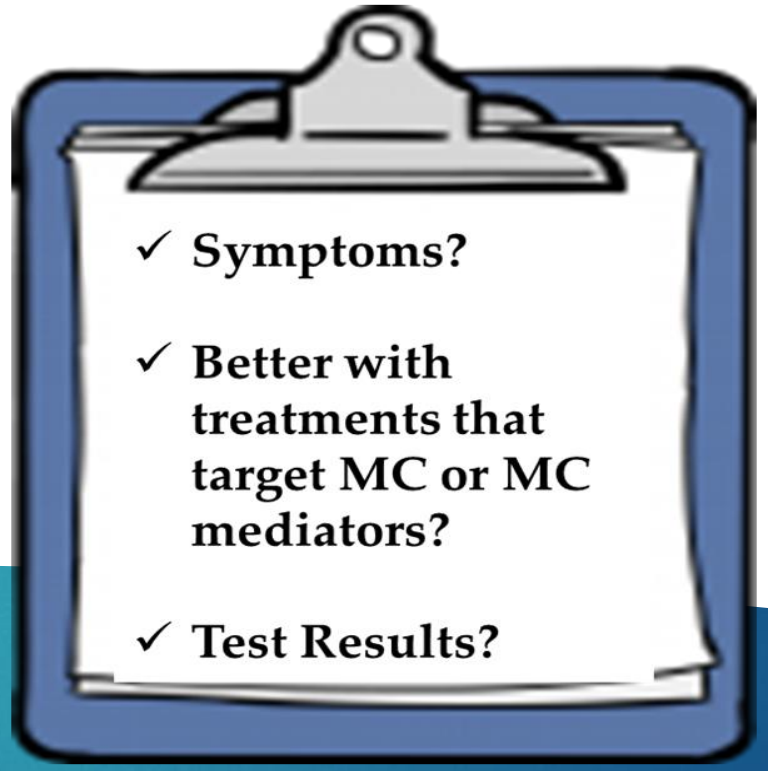
Mast Cells, Mastocytosis, and Related Disorders

Theoharis C. Theoharides, Ph.D., M.D., Peter Valent, M.D., and Cem Akin, M.D., Ph.D.

MCADs



Diagnosis: MCAS Checklist



2 or MCADs = MCAS

Case report:

Got MCAS?

Maybe.

Years of itching!

- KL is a 55-year old Caucasian woman, who has coped with chronic hives and pruritis for 5+ years,
- 1st OV in 2012 with my practice, after 6 previous evaluations with dermatology and allergy specialists;
- she had tried cetirizine, fexofenadine, prednisone, montelukast, nortriptyline, topicals corticosteroids

KL's Past Medical History

- Headache disorder
- Asthma
- Rhinitis
- Anxiety
- Irritable bowel syndrome
- Fatigue

Diagnosis: MCAS Checklist

- ✓ **Symptoms?**
- ✓ **Better with treatments that target MC or MC mediators?**
- ✓ **Test Results?**

Criterion #1: MCAS diagnosis 2 or more organ systems impacted by MCA?

Mastocytosis

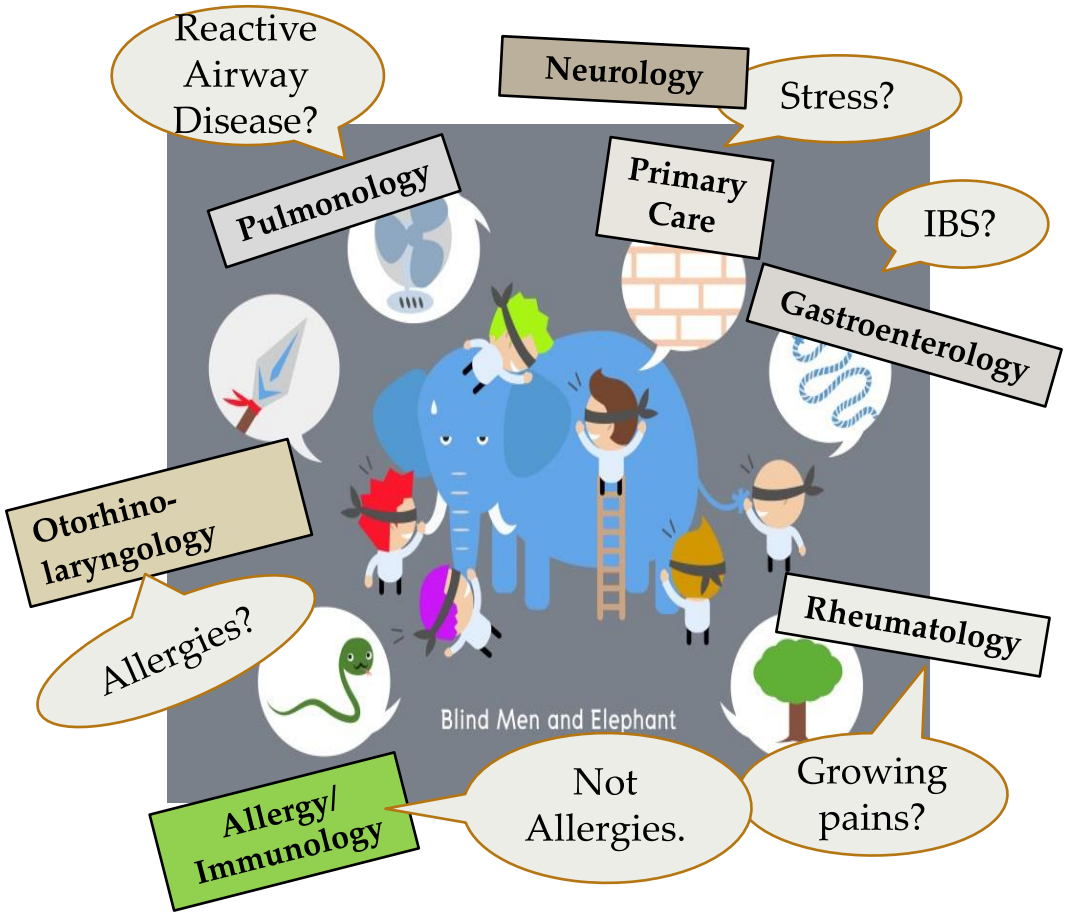
(Escribano et al, JACI 124:514)

Skin Lesions	90%
Pruritis	82%
Flushing	56%
Diarrhea	35%
Abdominal Cramping	30%
Neuropsychiatric Symptoms	**23%**
Anaphylaxis	23%
Peptic Symptoms	20%
Osteoporosis	18%
Hepatomegaly	12%
Splenomegaly	8%

Nonclonal Mast cell activation disorders

Hamilton, J allergy clin immunol 128;147

Abdominal Pain	94%
Dermatographism	89%
Flushing	89%
Headache	83%
Neuropsychiatric	**67%**
Diarrhea	67%
Rhinitis (Naso-ocular)	39%
Asthma	39%
Anaphylaxis	17%



KL's Family History

- Mother:

  headache disorder, hypertension
- Son: Rhinitis
- Daughter: IBS

TABLE II. Signs and symptoms of patients with MCAS

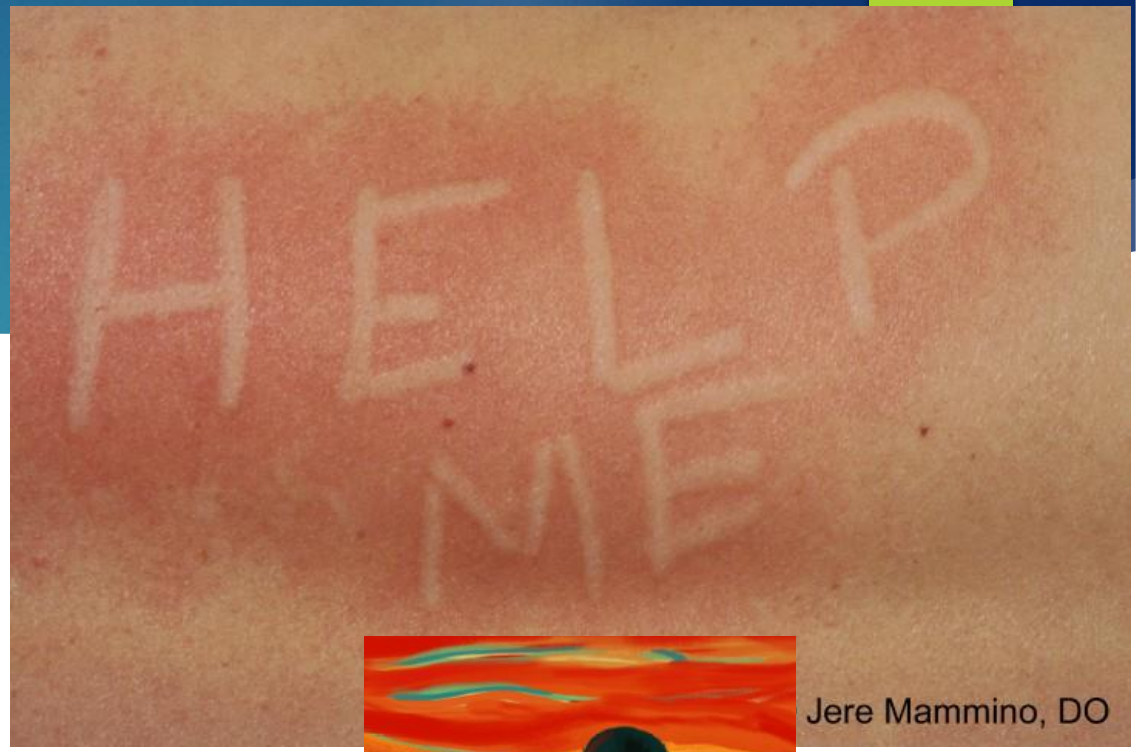
Sign or symptom	Total (%), n = 18
Abdominal pain	17 (94)
Dermatographism	16 (89)
Flushing	16 (89)
Headache	15 (83)
Poor concentration and memory	12 (67)
Diarrhea	12 (67)
Naso-ocular	7 (39)
Asthma	7 (39)
Anaphylaxis	3 (17)

Mast cell activation syndrome: A newly recognized disorder with systemic clinical manifestations

Matthew J. Hamilton, MD,[a] Jason L. Hornick, MD, PhD,[b] Cem Akin, MD, PhD,[a] Mariana C. Castells, MD, PhD,[a] and Norton J. Greenberger, MD[a] *Boston, Mass*

KL's Physical Exam

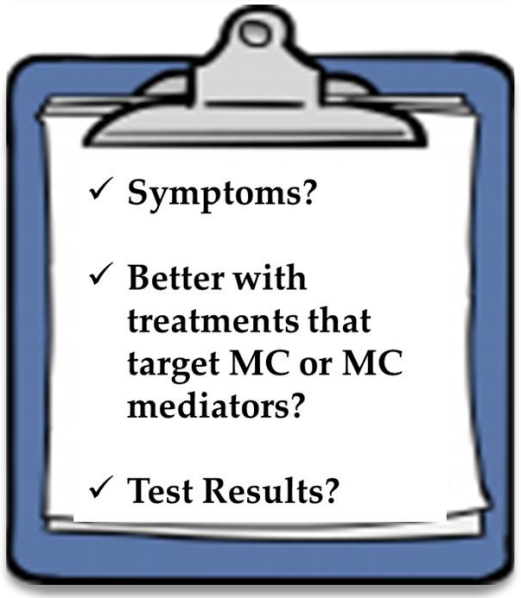
- General observations: thin female, chronically ill
- HEENT: turbinate hypertrophy, no adenopathy (swollen glands in the neck)
- GI: mild distension
- CV: Heart rate in 90s, regular
- Skin: Dermatographism
- Psychiatric: anxiety



DEVIL'S ITCH

Criterion #2: MCAS diagnosis Better with medications that target MCs or MC derived mediators?

Diagnosis: MCAS Checklist



KL had tried combinations of

- cetirizine, fexofenadine,
- montelukast,
- nortriptyline,

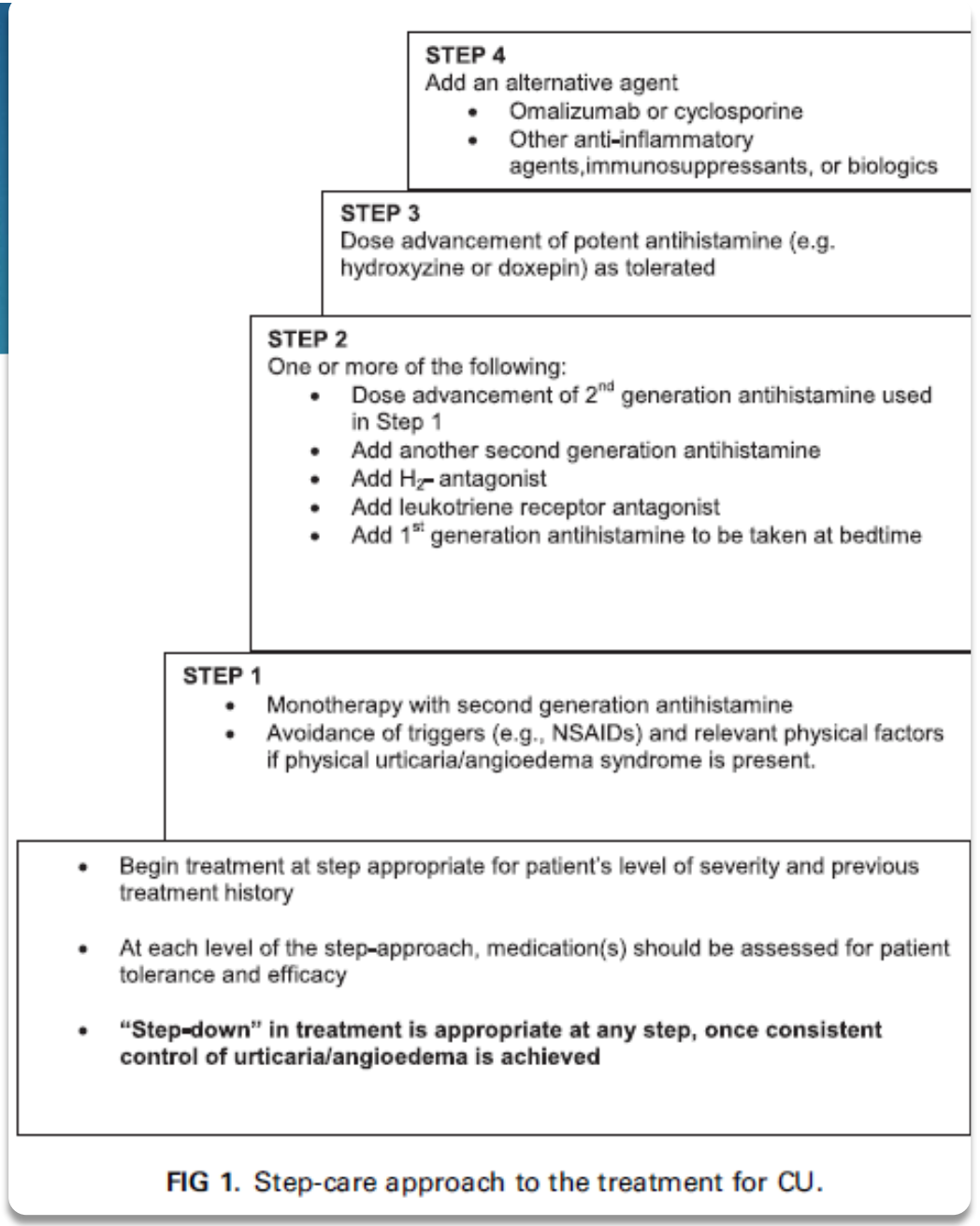


FIG 1. Step-care approach to the treatment for CU.

Alternative Agents in Refractory Urticaria

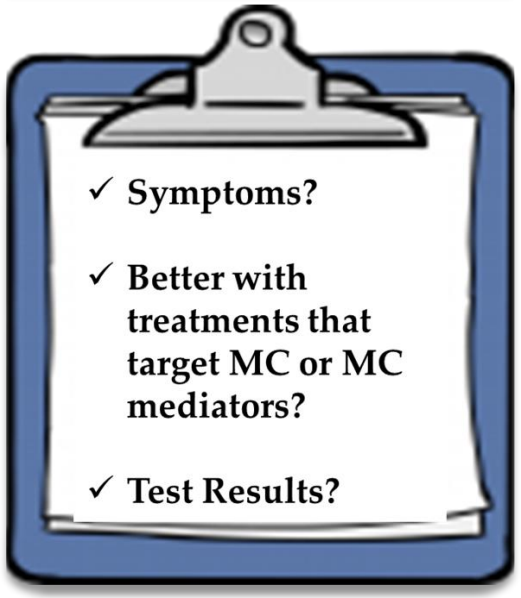
Khan J Allergy Clin Immunol 2013

TABLE I. Selected alternative agents for refractory chronic urticaria

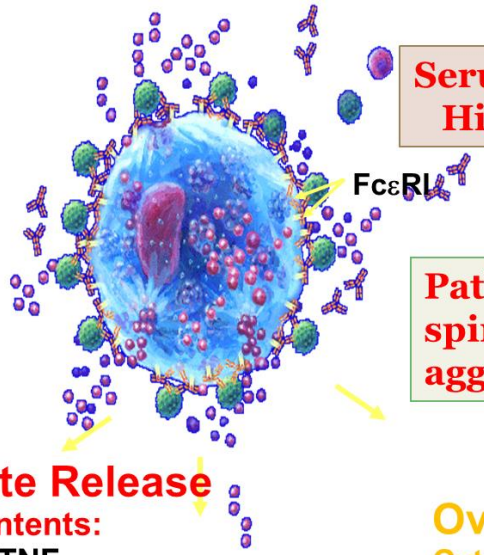
Alternative agent	Typical dose	Onset of improvement	Estimated effectiveness	Evidence
Anti-inflammatory agents				
Montelukast	10 mg daily	2-4 wk	Low	Multiple RCT (mixed results
Hydroxychloroquine	200 mg twice daily	Up to 12 wk	Moderate	1 RCT
Dapsone	100 mg daily with reduction of dose as tolerated	1-6 wk	Moderate	1 RCT
Sulfasalazine	500 mg twice daily, increasing to 1 g twice daily	<4 wk	Moderate	Case series
Methotrexate	10-15 mg weekly	1-6 mo	Moderate	Case series
Colchicine	0.6 mg twice daily	Unclear	Low-moderate	Case series
Immunosuppressant agents				
Cyclosporine				
Low dose	1-2 mg/kg/d	<4 wk	Moderate-high	Case series
Higher dose	3-5 mg/kg/d	1-7 d	High	2 RCTs
Tacrolimus	1 mg twice daily, increasing to 2-3 mg twice/d if needed	1-2 wk	High	Case series
Mycophenolate	1000 mg twice daily, increasing to 4-6 g/d if needed	1-9 wk	Moderate	Case series
Immunomodulatory agents				
Omalizumab	150-300 mg every 4 wk	1-2 wk	High	3 RCTs
Immune globulin	150-400 mg/kg every 4 wk or daily × 5 d	High dose: 2 wk Low dose: 4-5 mo	Moderate	Case series

Criterion #3: MCAS diagnosis
suspected MCA events associated with an elevation in validated mast cell markers

Diagnosis: MCAS Checklist



Serum Tryptase



Serum, Urine Histamine

Pathology- spindle MC, MC aggregates

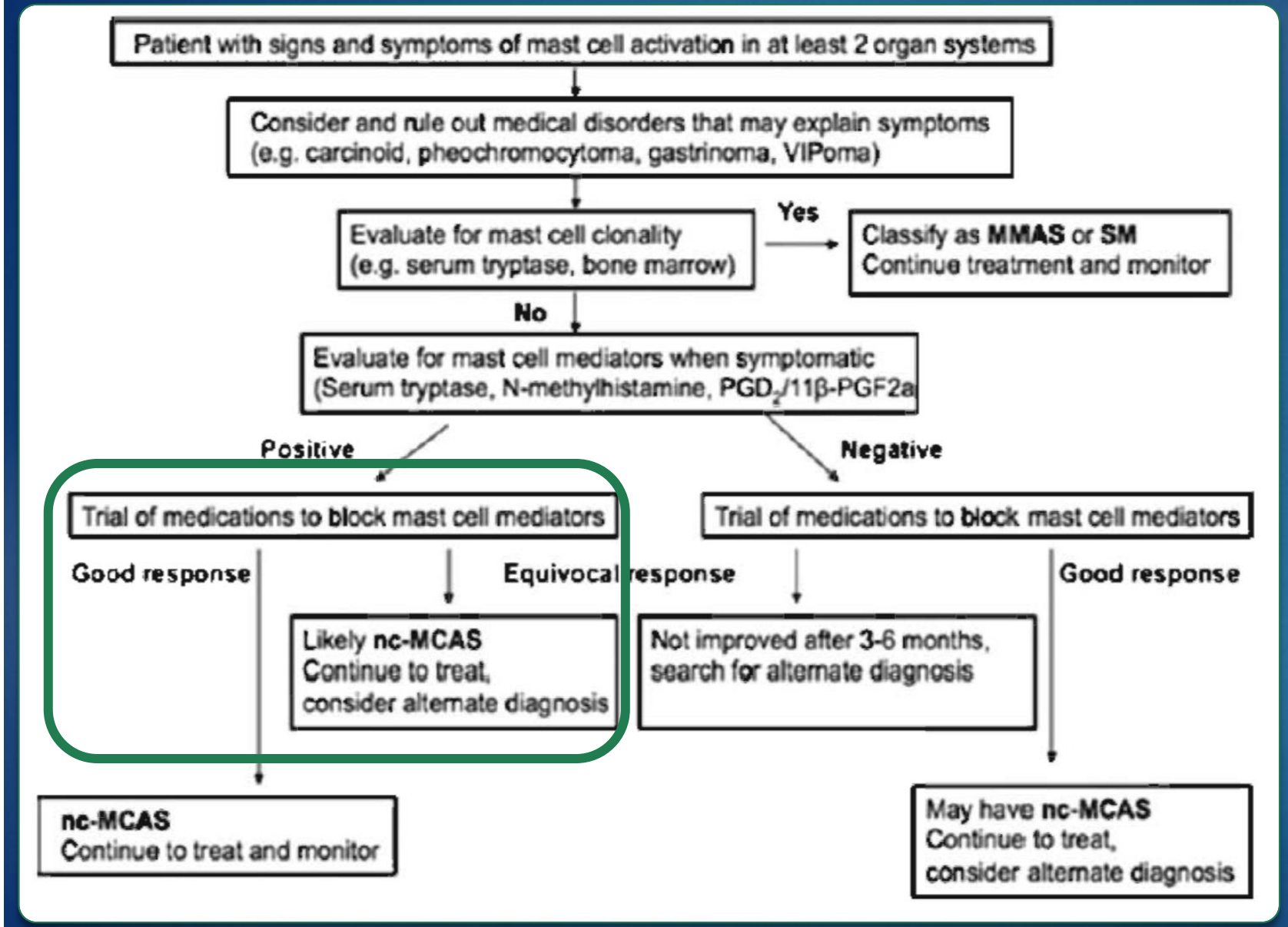
Immediate Release
Granule contents:
Histamine, TNF-α, Proteases, Heparin

Urine PGD2, 11-beta PGF2

Over Minutes
Lipid mediators:
Prostaglandins
Leukotrienes

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

CD2, CD25 Expression



Tryptase

SM: tryptase >20

Nonclonal MCAS
20% +2 ng/mL increase from the baseline

Hyper-alphatryptasemia:
Genetic study
Serum Tryptase > 7 ng/ml

Allergen testing Celiac Panel EGD/ Colonoscopy

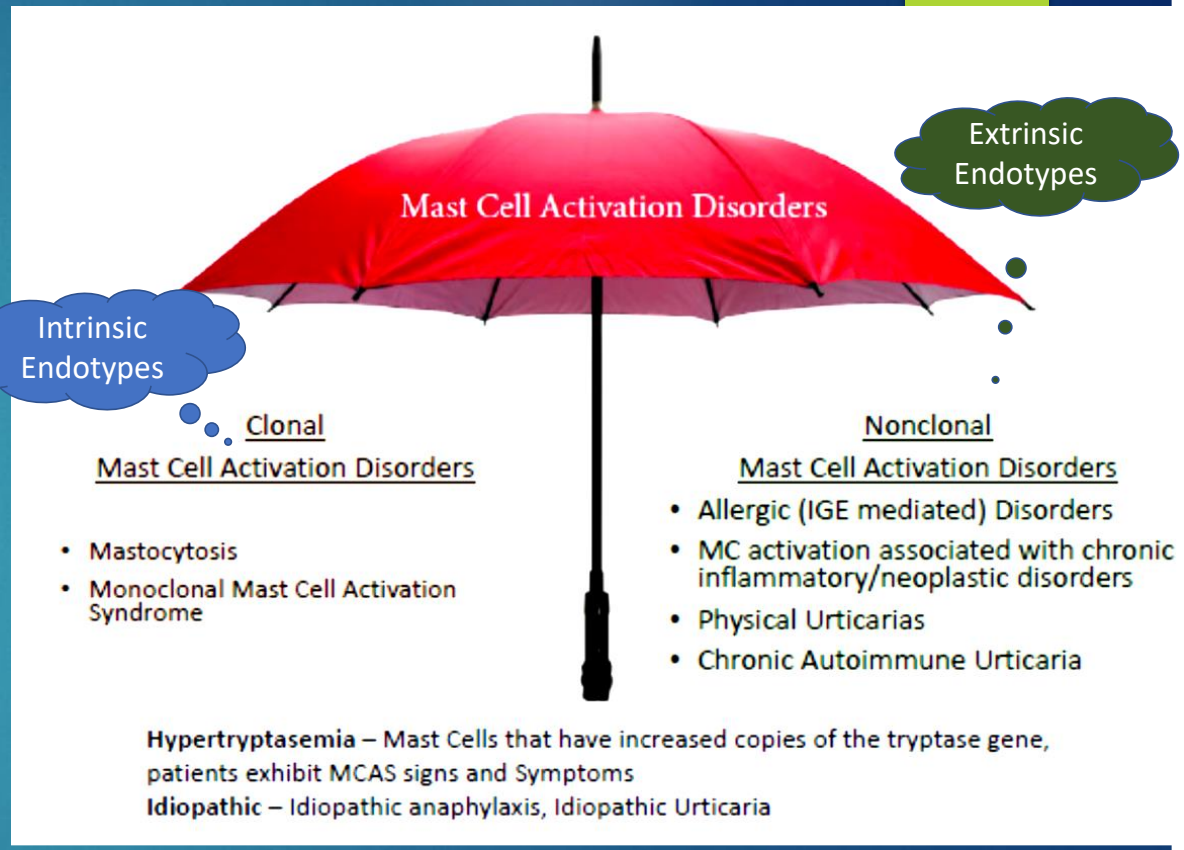
- Some food (wheat/gluten, peanuts, eggs, nuts and shellfish, milk*, egg*, soy*)
- Medications
- Airbone Allergens
- Insect stings or bites
- Autoimmune Disorders
- Infections
- Physical stimuli, such as pressure, cold, heat, exercise or sun exposure

Allergen testing

PIDD evaluation Primary Immune Deficiency Disorder

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

Connective Tissue Disorder EDS Screen



Primary & Secondary MCAD

JK's Health Intake Questionnaire: Her Story

	Absent	Very Mild	Mild	Moderate	Severe	Very Severe
Facial pain/pressure	0	1	2	(3)	4	5
Facial congestion/fullness	0	1	2	3	(4)	5
Nasal obstruction/blockage	0	1	2	(3)	4	5
Discolored or pus nasal discharge or post-nasal drip	0	1	2	(3)	4	5
Decreased sense of smell	0	1	(2)	3	4	5
Headache	0	1	2	(3)	4	5
Fever	0	1	(2)	3	4	5
Halitosis (bad breath)	0	(1)	2	3	4	5
Fatigue (tiredness)	0	1	2	3	(4)	5
Dental pain	0	1	2	3	(4)	5
Cough	0	1	2	3	(4)	(5)
Ear pain/pressure/fullness	0	1	(2)	3	4	5

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

Nasal steroid sprays (Vancenase, Flonase, Nasonex, Rhinocort, Nasacort, etc)
I currently use these medications (Y) N
I used these medications for a total of 2 weeks in the last 12 months

Anti-histamines (Allegra, Claritin, Zyrtec, etc)
I currently use these medications (Y) N
I used these medications for a total of everydays weeks in the last 12 months

Antibiotics
Number of courses in last 12 months 5-6
I spent a total of 5-6 weeks on antibiotics in the last 12 months
My longest course of antibiotics lasted 10 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 20 days of work/school due to nasal problems

In the last 12 months, I did not leave home for (a) weeks days due to my nasal problems

In the last 12 months, I visited a doctor or nurse 7 times for my nasal problems

In the last 12 months, I had 7 acute infections of my nose/sinuses

(practitioners) Don't Ask, (patients) Don't Tell

KL'S LAB VALUES MAST CELL TRIGGERS

Low Total Serum IGE

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
CBC With Differential/Platelet					
WBC	6.7		x10E3/uL	4.0 - 10.5	01
RBC	4.01		x10E6/uL	3.77 - 5.28	01
Hemoglobin	12.2		g/dL	11.1 - 15.9	01
Hematocrit	37.9		%	34.0 - 46.6	01
MCV	95		fL	79 - 97	01
MCH	30.4		pg	26.6 - 33.0	01
MCHC	32.2		g/dL	31.5 - 35.7	01
RDW	13.6		%	12.3 - 15.4	01
Platelets	293		x10E3/uL	140 - 415	01
Neutrophils	70		%	40 - 74	01
Lymphs	23		%	14 - 46	01
Monocytes	6		%	4 - 13	01
Eos	1		%	0 - 7	01
Basos	0		%	0 - 3	01
Neutrophils (Absolute)	4.7		x10E3/uL	1.8 - 7.8	01
Lymphs (Absolute)	1.5		x10E3/uL	0.7 - 4.5	01
Monocytes(Absolute)	0.4		x10E3/uL	0.1 - 1.0	01
Eos (Absolute)	0.0		x10E3/uL	0.0 - 0.4	01
Baso (Absolute)	0.0		x10E3/uL	0.0 - 0.2	01
Immature Granulocytes	0		%	0 - 2	01
Immature Grans (Abs)	0.0		x10E3/uL	0.0 - 0.1	01

Immunoglobulin E, Total	9		IU/mL	0 - 100	01
Complement, Total (CH50)	**63**	**High**	U/mL	22 - 60	01

Tissue Inflammation??

Allergen-Specific IGE

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 herbaru	<0.08		kU/L
M003-IgE Aspergillus fumigatu	**0.08**	**Abnormal**	kU/L
M004-IgE Mucor racemosus	<0.08		kU/L
M006-IgE Alternaria tenuis	<0.08		kU/L
M010-IgE Stemphylium botryosu	**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			

KL's Lab test results

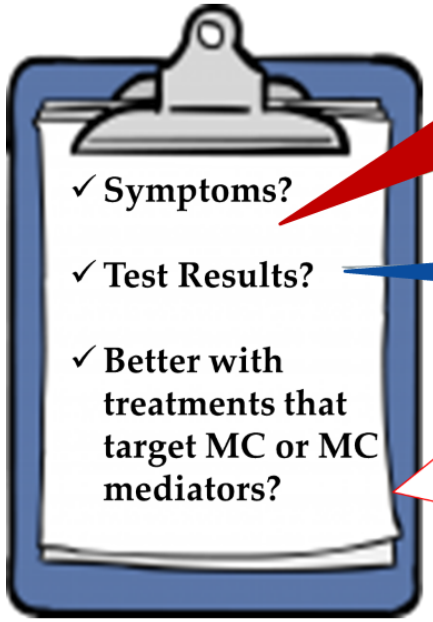
Thyroid Panel With TSH			
TSH	1.360	uIU/mL	0.450 - 4.500
Thyroxine (T4)	6.1	ug/dL	4.5 - 12.0
T3 Uptake	30	%	24 - 39
Free Thyroxine Index	1.8		1.2 - 4.9
Thyroid Antibodies			
Thyroid Peroxidase (TPO) Ab	11	IU/mL	0 - 34
Antithyroglobulin Ab	<20	IU/mL	0 - 40
Siemens (DPC) ICMA Methodology			
Chronic Urticaria			
cu index	**>50.0 High**		<10.0
The CU Index(R) test is the second generation Functional Anti-FCeR 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	10	IU/mL	0 - 100
Tryptase	9.3	ug/L	2.2 - 13.2

IgE receptor auto-antibodies

Trytpase >6 mcg/ml or higher, Hyper-alphatryptasemia?

Immunoglobulins A/G/M, Qn, Ser			
Immunoglobulin G, Qn, Serum	532 Low	mg/dL	700 - 1600
Immunoglobulin A, Qn, Serum	85	mg/dL	70 - 400
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	221	mg/dL	40 - 230

Hypogammaglobulinemia



Rhinitis
Urticaria
Asthma
Neuropsychiatric dx

Tryptase 9.3
+ve CU panel
EGD – 40 MC/hpf

Tried diphenhydramine, cetirizine, ranitidine, clemastine, cimetidine, loratadine – "my life is H*** 24-7, 365 days of the year"

1. Eight or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or elsewhere on skin, after age 1.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections.
10. A family history of Primary Immunodeficiency.

KL = Secondary Mast Cell Activation Disorders

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *The Year in Human and Medical Genetics: Inborn Errors of Immunity*

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

Peter D. Arkwright[1] and Andrew R. Gennery[2]

KL's MCAD treatments

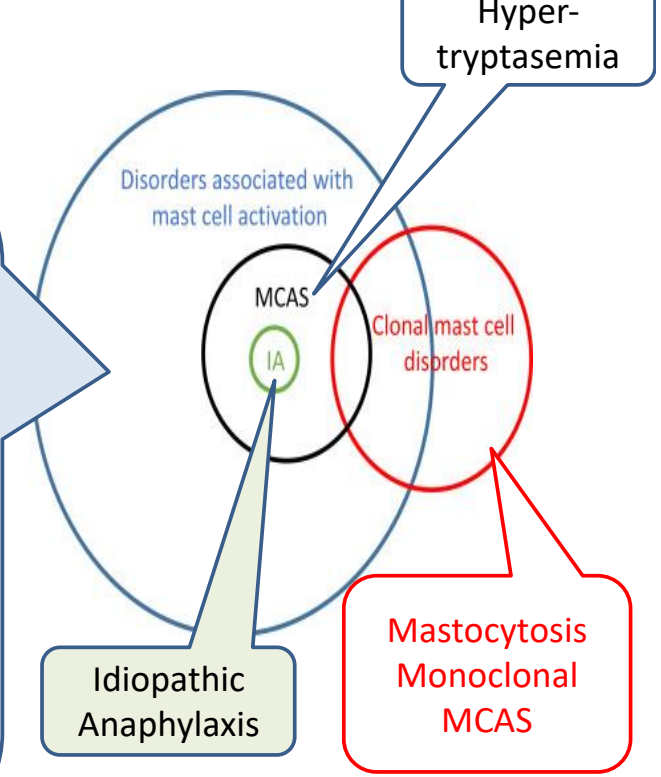
KL's Treatment Recommendations:

Azithromycin prophylaxis, Colostrum, Probiotics, Histamine and Leukotriene Blockade

*

IVIG

- 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**

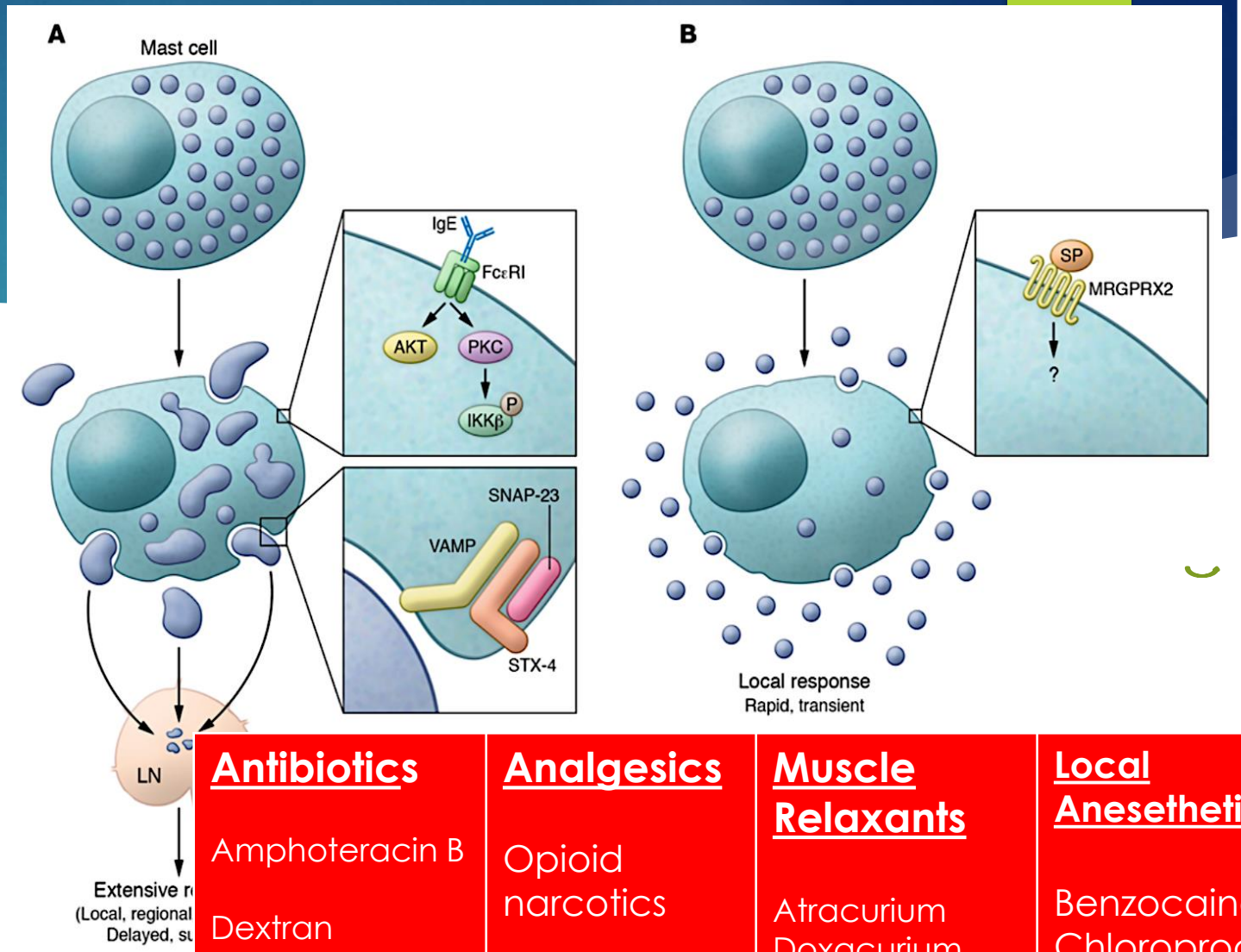


Allergen-IgE	Infections	Primary Immune Deficiency	Autoimmune Disorders
Avoidance measures (Diet, Environment) Medications: histamine blockade Desensitization (Immunotherapy) Omalizumab, Dupilumab Anti-interleukin mAb	Hepatitis, Lyme, Borrelia, EBV, HSV	Prophylactic Antibiotics Immune Globulin Anti-inflammatory Agents	Anti-inflammatory Agents Immune Globulin

Better Tolerated in MCAD patients

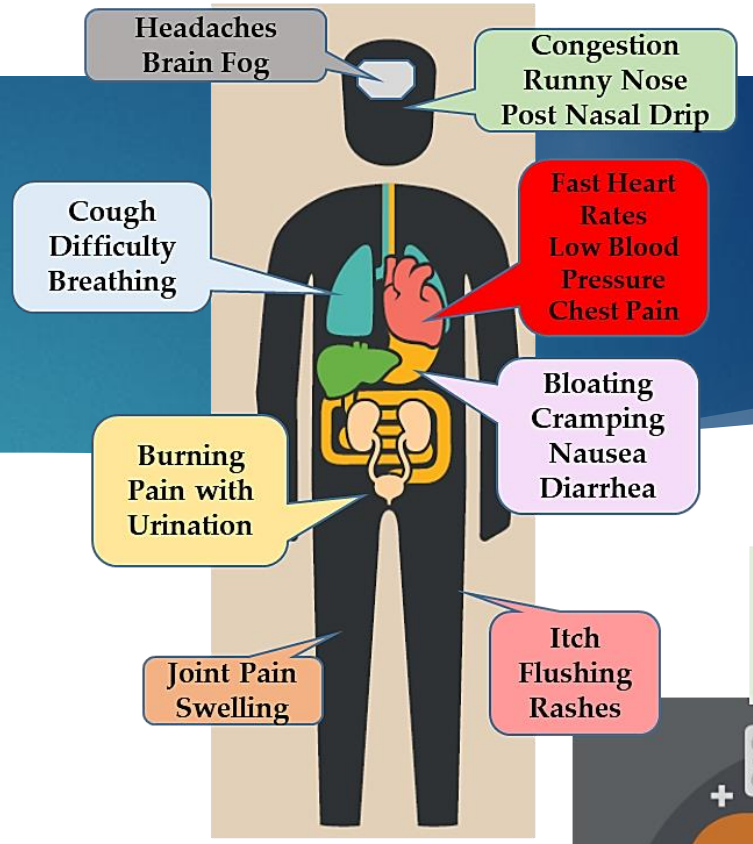
- **Pain Medications:**
  - Fentanyl (may require adjunct treatment with Zofran), Tramadol, Nucynta
- **Muscle relaxants:**
  - pancurorium, vercuronium
- **Local Anesthetics:**
  - Bupivacaine, Lidocaine, Mepicacaine, Prilocaine, Levobupivacaine, Ropivacaine
- **Intraoperative Induction:**
  - Ketamine,Midazolam, Propofol
- **Inhaled Anesthetics:**
  - Sevoflurane
- **Benzodiazepenes:**
  - lorazepam, diazepam, temazepam

Medication Allergies/Intolerance



Antibiotics	Analgesics	Muscle Relaxants	Local Anesethetics
Amphoteracin B	Opioid narcotics	Atracurium	Benzocaine,
Dextran	NSAIDs	Doxacurium	Chloroprocaine, Procaine,
Vancomycin		D-tubocurarine	Tetracine
		Metocurine	
		Mivacurium	
		Succinylcholine	

Mast Cell Activation Syndrome - Defined. (2019)

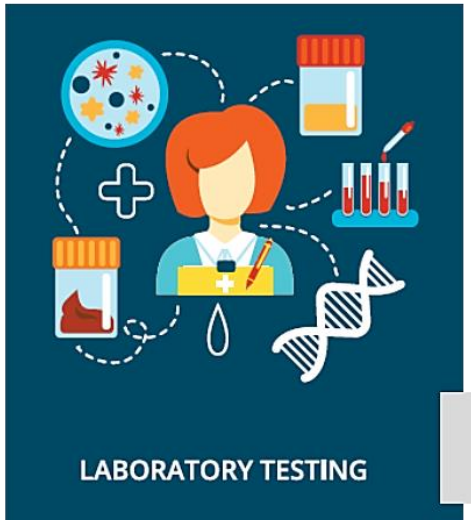


#1
Symptoms?

Criteria for MCAS Diagnosis:

1. Do you have symptoms impacting 2 or more organs?
2. Do you feel better with treatments that lessen the effects of Mast Cell actions and/or and Mast Cell derived mediators?
3. Show the data: detection of increased Mast Cell activity or sustained presence of MC derived mediators?

#2
Response to medications?



#3
Positive lab tests?

Immunol Allergy Clin North Am. 2018 August ; 38(3): 469–481. doi:10.1016/j.iac.2018.04.002.

Non-Clonal Mast Cell Activation: A Growing Body of Evidence

Matthew J. Hamilton, M.D.
Assistant Professor, Harvard Medical School, Division of Gastroenterology, Hepatology, and Endoscopy, Brigham and Women's Hospital, Boston, MA. U.S.A.

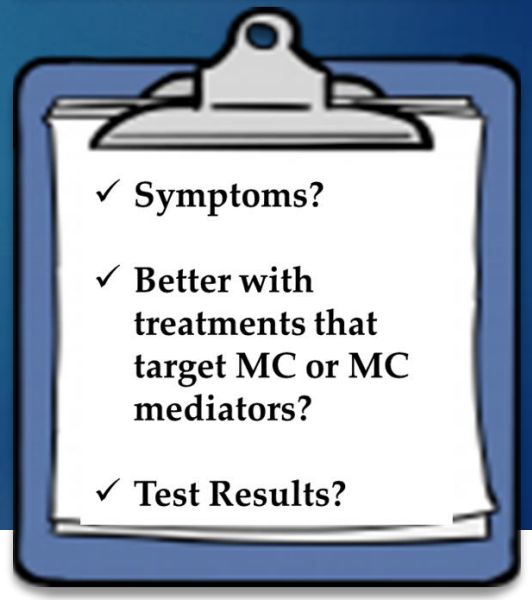
Patients who present with typical features of MCA, with laboratory confirmation, and without evidence of a clonal mast cell disorder should be initiated on MC targeted treatment.

If a major response is achieved, a diagnosis of non-clonal mast cell activation syndrome (NC-MCAS) is likely and treatment should be optimized.

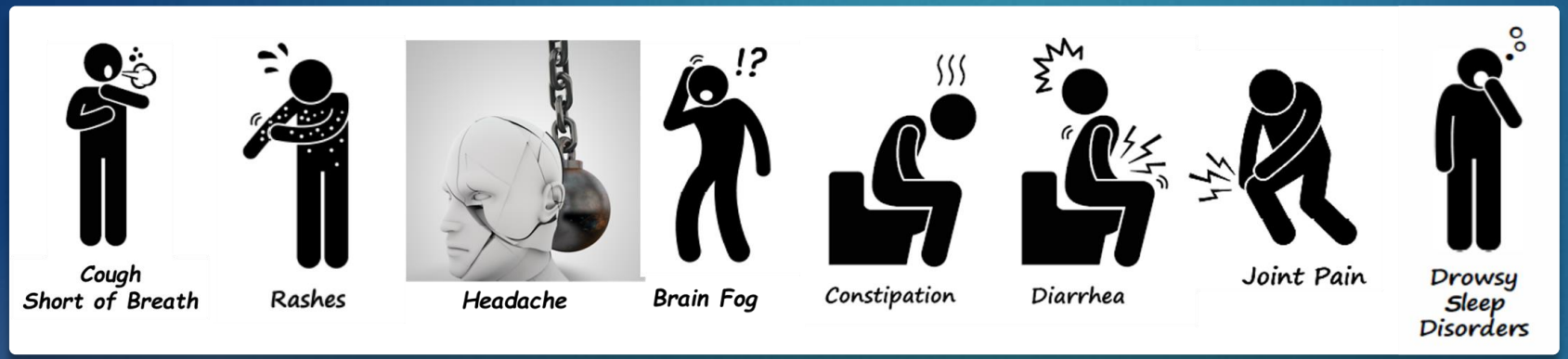
In search of MCAS:

Lessons from Tarrytown

Diagnosis: MCAS Checklist



Not MCAS, but still reacting

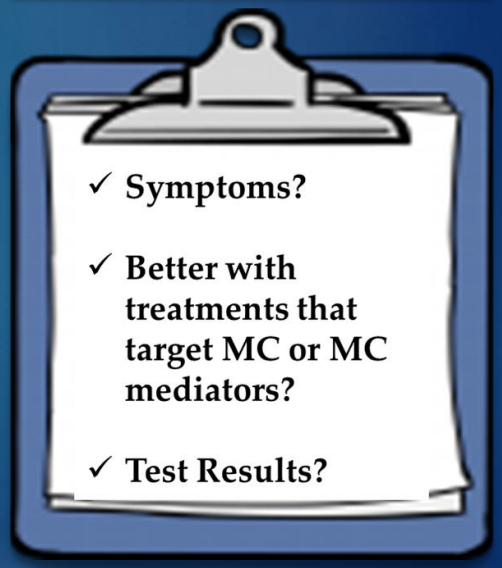


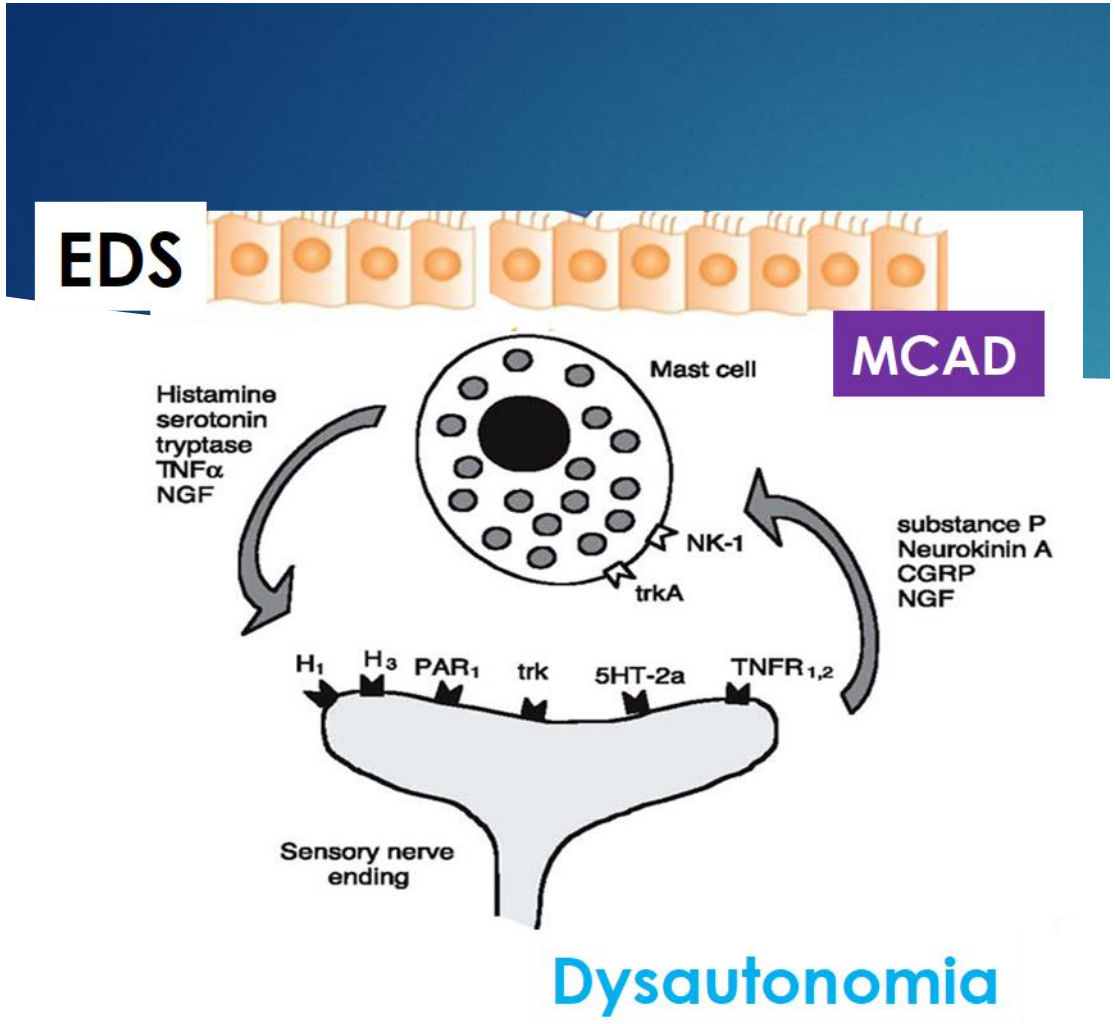
The MCA diagnosis is sometimes applied to patients with vague yet suggestive symptoms.

These patients may suffer from an unrelated, overlooked disease or syndrome.

Applying solid diagnostic criteria when considering the MCA diagnosis helps avoid wasting time and money.

Diagnosis: MCAS Checklist





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: Primary Immune deficiencies; Auto-inflammatory disorders such as deficiency of inter-leukin-1–receptor antagonist*; Familial hyper-IgE syndrome Vasculitis*

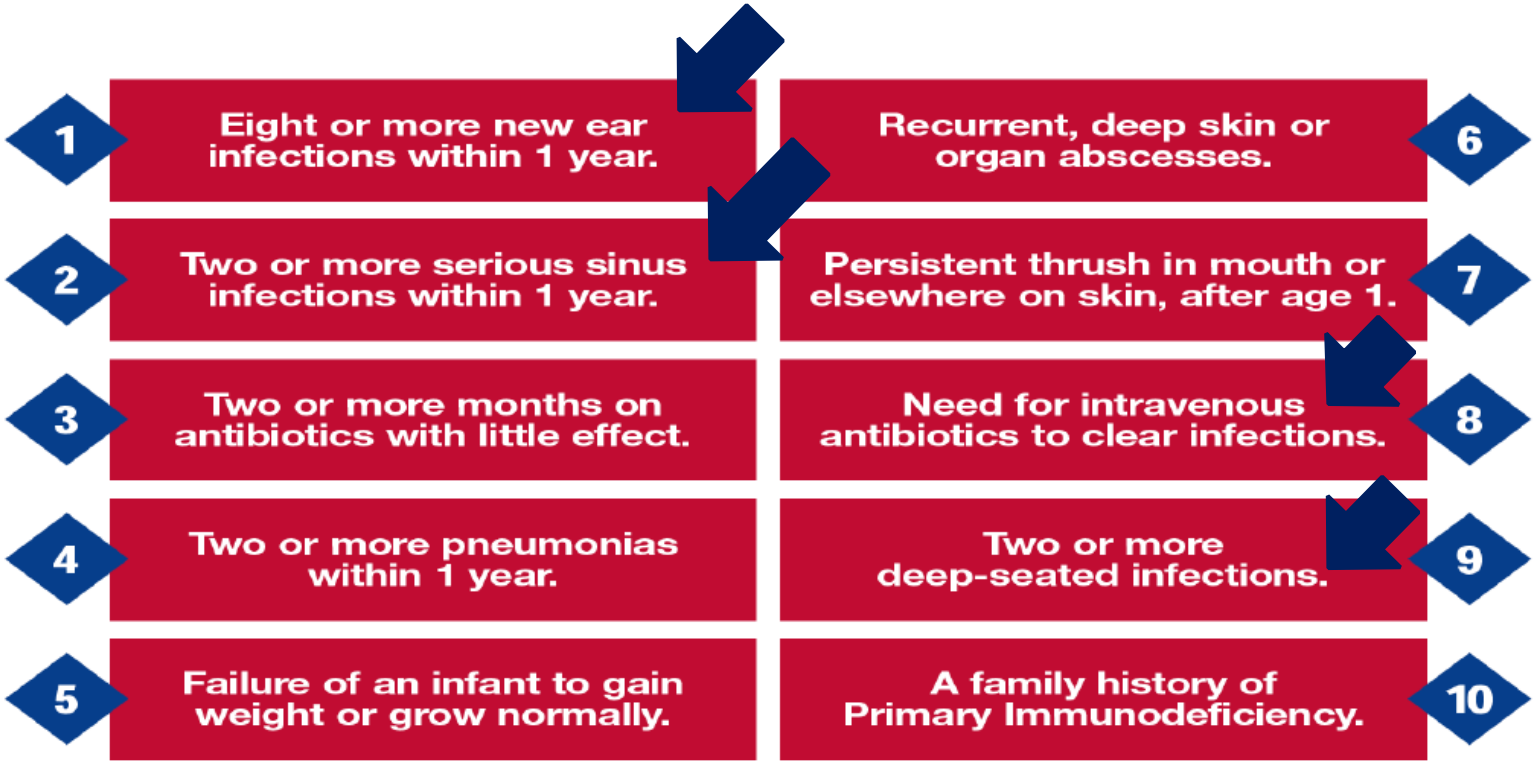
psychiatric conditions Anxiety; Depression; Headaches; Mixed organic brain syndrome;

Neurologic/ Chronic fatigue syndrome Somatization disorder; Multiple sclerosis Autonomic dysfunction;

Skin Conditions: Angioedema* Atopic dermatitis* Chronic urticaria* Scleroderma*, and

Connective Tissue disorders: Ehlers Danlos Syndromes

FEATURES OF MCAD IN PATIENTS WITH UNDIAGNOSED IMMUNODEFICIENCY



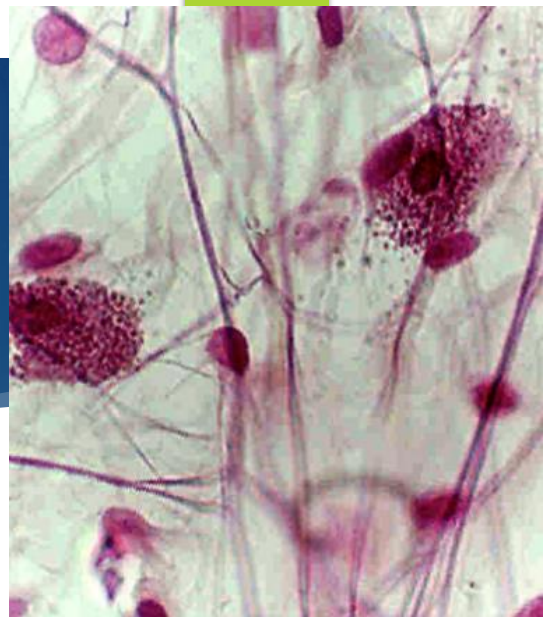
already diagnosed

Screening questionnaire for an immune deficiency syndrome/disorder:

Have you or your child been treated for 4 or more new ear infections within 1 year?
Have you or your child been treated for 2 or more serious sinus infections within 1 year?
Have you or your child received 2 or more months on antibiotics with little effect?
Have you or your child been treated for Two or more pneumonias within 1 year?
Did you or your child have a history of failure of an infant to gain weight or grow normally?
Have you or your child been treated for recurrent, deep skin or organ abscesses?
Have you or your child been treated for persistent or recurrent thrush in mouth or fungal infection on skin
Have you or your child needed for intravenous antibiotics to clear infections?
Have you or your child been treated for 2 or more deep-seated infections including septicemia (blood infection)?
Have you ever been evaluated for recurrent fevers (fevers of unknown origin)?
Has a family member been treated for recurrent or severe infections, diagnosed with primary immune deficiency disorder?

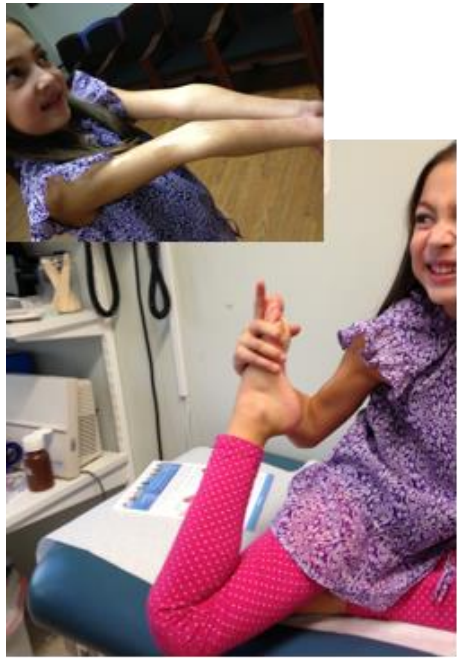
Clinical Allergy, 1977, Volume 7, page 203

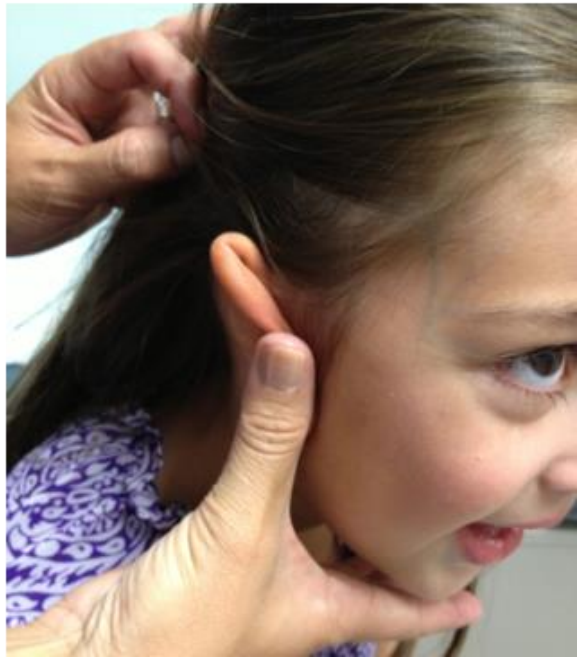
An early observation of a possible relationship between connective tissue and mast cells and allergic (Allergen triggered MCA)
1977



Letter to the Editor

Atopy in Connective Tissue Disorders





Inherited Connective Tissue Disorders and Mast Cell Activation Syndromes

American Journal of Medical Genetics Part C (Seminars in Medical Genetics)

RESEARCH REVIEW

Mast Cell Disorders in Ehlers–Danlos Syndrome

SURANJITH L. SENEVIRATNE, ANNE MAITLAND, * AND LAWRENCE AFRIN

Well known for their role in allergic disorders, mast cells (MCs) play a key role in homeostatic mechanisms and surveillance, recognizing and responding to different pathogens, and tissue injury, with an array of chemical mediators. After being recruited to connective tissues, resident MCs progenitors undergo further differentiation, under the influence of signals from surrounding microenvironment. It is the differential tissue homing and local maturation factors which result in a diverse population of resident MC phenotypes. An abundance of MC reside in connective tissue that borders with the external world (the skin as well as gastrointestinal, respiratory, and urogenital tracts). Situated near nerve fibers, lymphatics, and blood vessels, as well as coupled with their ability to secrete potent mediators, MCs can modulate the function of local and distant structures (e.g., other immune cell populations, fibroblasts, angiogenesis), and MC dysregulation has been implicated in immediate and delayed hypersensitivity syndromes, neuropathies, and connective tissue disorders (CTDs). This report reviews basic biology of mast cells and mast cell activation as well as recent research efforts, which implicate a role of MC dysregulation beyond atopic disorders and in a cluster of Ehlers–Danlos Syndromes, non-IGE mediated hypersensitivity disorders, and dysautonomia.

209 **A New Disease Cluster: Mast Cell Activation Syndrome, Postural Orthostatic Tachycardia Syndrome, and Ehlers-Danlos Syndrome**

Ingrid Cheung, Peter Vadas, MD, PhD; St. Michael's Hospital, Toronto, ON, Canada.

RATIONALE: Patients with postural orthostatic tachycardia syndrome (POTS) and hypermobility often describe symptoms suggestive of mast cell activation. Herein, we describe a new, unique phenotype, characterized by the co-segregation of three disorders: POTS, Ehlers Danlos syndrome (EDS) and mast cell activation syndrome (MCAS).

METHODS: Participants with diagnoses of POTS and EDS were recruited from throughout North America through a patient support group and evaluated by questionnaire and supporting documentation. A formal diagnosis of POTS by a cardiologist included confirmation via tilt-table test. A formal diagnosis of EDS required assessment by a dermatologist, a Beighton score of ≥ 5/9 and a diagnostic skin biopsy. A questionnaire for MCAS was based on diagnostic criteria and validated symptoms as reported by Akin, Valent and Metcalfe (2010).

RESULTS: 15 participants completed questionnaires with required documentation. All eligible participants were female. 12 of these people had formal diagnoses of POTS (80%), 9 were diagnosed with both POTS and EDS. 6 of 9 patients with both POTS and EDS had validated symptoms of a mast cell disorder (66%), suggestive of MCAS.

CONCLUSIONS: From these pilot data, it appears that a mast cell disorder may frequently co-segregate with POTS and a collagen disorder such as EDS.

ABSTRACT NUMBER: 2115

Mast Cell Activation Features in Ehlers-Danlos/Joint Hypermobility Patients: A Retrospective Analysis in Light of an Emerging Disease Cluster

Dave Lee[1] and Eric Mueller[2], [1]Arthritis Northwest, PLLC, Spokane, WA, [2]Discus Analytics LLC., Spokane, WA

Meeting: 2017 ACR/ARHP Annual Meeting

Date of first publication: September 18, 2017

Keywords: Ehlers-Danlos syndrome, fibromyalgia, hypermobility and mast cells

Received: 20 March 2018 | Revised: 23 November 2018 | Accepted: 3 February 2019

DOI: 10.1002/ccr3.2210

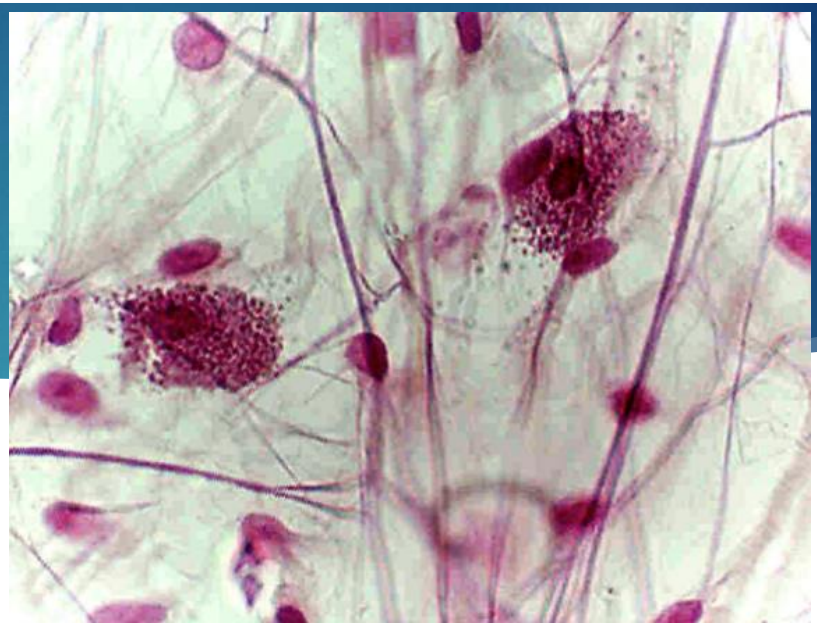
CASE REPORT

WILEY Clinical Case Reports

Hypermobile type Ehlers-Danlos syndrome associated with hypogammaglobulinemia and fibromyalgia: A case-based review on new classification, diagnosis, and multidisciplinary management

Wei Zhang[1] | Kevin Windsor[2] | Richard Jones[1,2] | David Oscar Taunton[1]

MCAD and EDS?



Our findings link findings (germline) duplication in TPSAB1 (the alpha-tryptase gene) with

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

nature genetics

Elevated basal serum tryptase identifies a multisystem disorder associated with increased *TPSAB1* copy number

Jonathan J Lyons[1], Xiaomin Yu[1], Jason D Hughes[2], Quang T Le[3], Ali Jamil[1], Yun Bai[1], Nancy Ho[4], Ming Zhao[5], Yihui Liu[1], Michael P O'Connell[1], Neil N Trivedi[6,7], Celeste Nelson[1], Thomas DiMaggio[1], Nina Jones[8], Helen Matthews[9], Katie L Lewis[10], Andrew J Oler[11], Ryan J Carlson[1], Peter D Arkwright[12], Celine Hong[10], Sherene Agama[1], Todd M Wilson[1], Sofie Tucker[1], Yu Zhang[13], Joshua J McElwee[2], Maryland Pao[14], Sarah C Glover[15], Marc E Rothenberg[16], Robert J Hohman[5], Kelly D Stone[1], George H Caughey[6,7], Theo Heller[4], Dean D Metcalfe[1], Leslie G Biesecker[10], Lawrence B Schwartz[3] & Joshua D Milner[1]

If 5 of 9 are present with a sensitivity of 99.6% and a specificity of 98% there is a form of EDS present:

- Peri-arthralgia (more then 1 joint more then 3 months)
- Fatigue (chronic, disabling more then 6 months)
- motor dysproprioception (the door sign)
- joint instability (subluxations, dislocations often autoreducing)
- skin fragility (atrophic scarring, delayed wound healing)
- Hypermobility (pos Beighton / 5 point historic questionnaire / pos glomerulo-humeral abduction above 95 degrees),
- gastro-esophageal reflux (treated)
- Ecchymosis (spontaneous)
- Hyperacusis (fragility to sounds below 50 decibel)

Hamonet C., *et al*. "Ehlers-Danlos Syndrome (EDS) - Contribution to Clinical Diagnosis - A Prospective Study of 853 Patients". *EC Neurology* 10.6 (2018).

Screening for CTDs: EDS/HSD

The **Ehlers–Danlos** Society™

THE BEIGHTON SCORE

How to Assess Joint Hypermobility

A numerical mobility score of 0 to 9, one point allocated for the ability to perform each of the following tests:

Pull little finger back beyond 90°
(one point for each side)

Pull thumb back to touch forearm
(one point for each side)

Bend elbow backwards beyond 10°
(one point for each side)

Bend knee backwards beyond 10°
(one point for each side)

Lie hands flat on floor while keeping knees straight and bending forward at waist

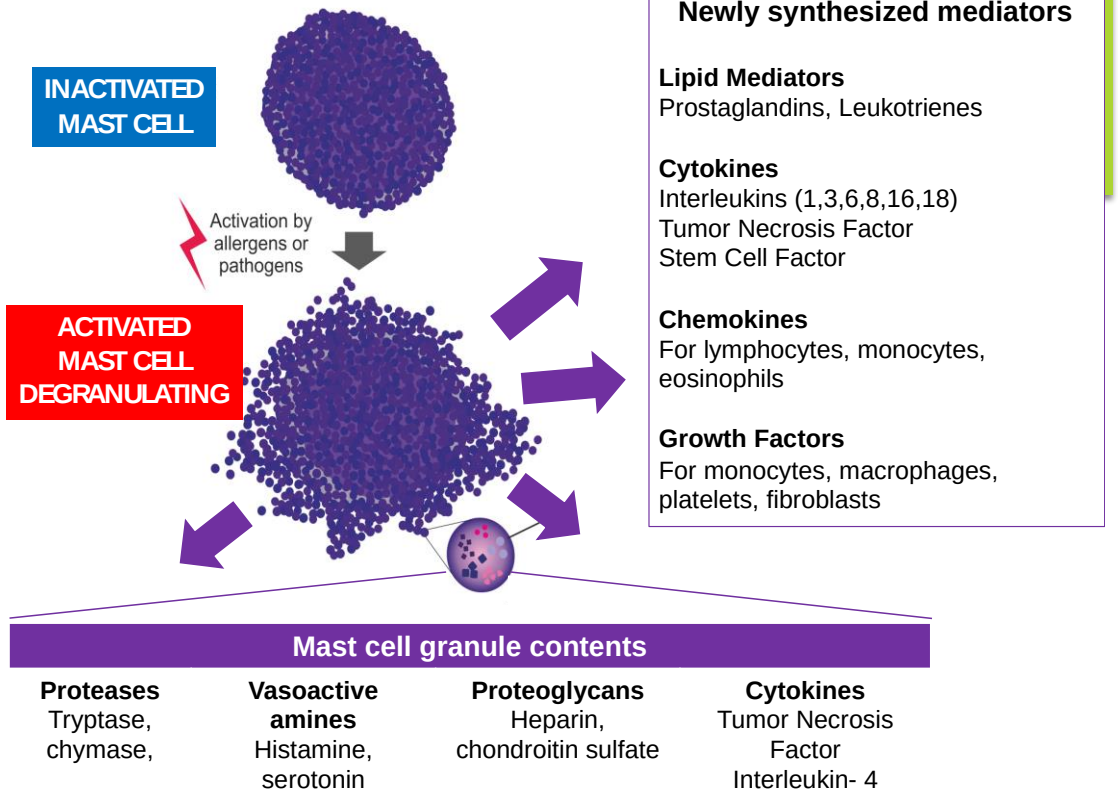
A positive Beighton score for adults is 5 out of the 9 possible points; for children, a positive score is at least 6 out of 9 points.

As joint mobility is known to decrease by age for adults, include historical information by asking, "Can you now or have you previously been able to..."

The Ehlers-Danlos Society
P.O. Box 87463
Montgomery Village, MD 20886
T: 410.670.7577

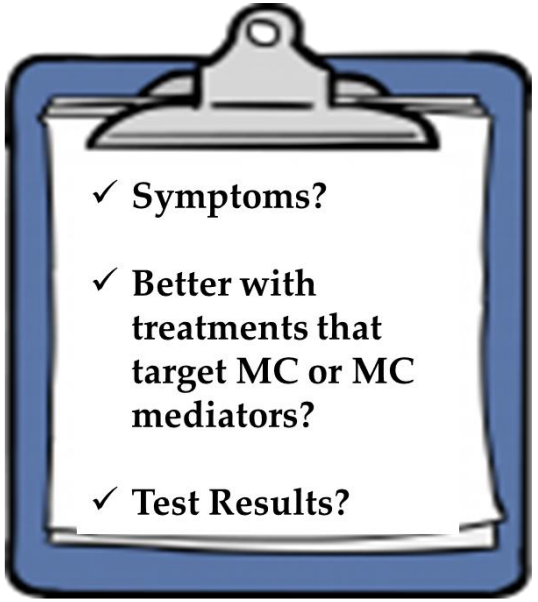
ehlers-danlos.com

Mast Cell Activation in Health and Disease



Primary	Secondary	Idiopathic
• Systemic Mastocytosis • Monoclonal Mast Cell Activation Syndrome	• Atopic disorders • Chronic non-atopic, immune mediated disorders (PID, A/I) • Neoplastic Disorders • Physical Urticarias • Chronic autoimmune urticaria	• Anaphylaxis • Angioedema • Urticaria

MCAD Diagnosis and treatment



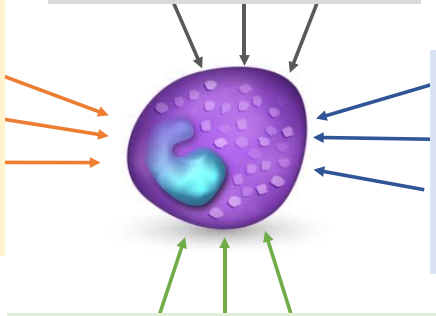
Mast Cell Triggers

Environmental Exposures

Chemicals
Stinging insect venom
Mercury
Lipopolysaccharide

Infectious Agents
Bacteria
Fungi
Viruses

Medications
Adenosine
Morphine
Muscle Relaxants
Nonsteroidal anti-inflammatory Agents, such as Ibuprofen and Aspiring
Vancomycin



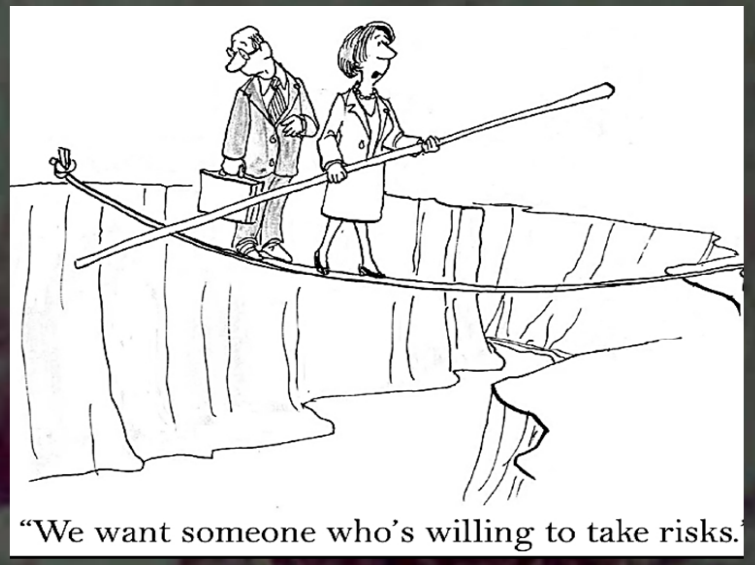
Amino Acid Peptide Messengers
Cortisol Releasing Hormone
Endorphins
Parathyroid Hormones
Vaso-active Intestinal Peptide
Thrombin
Endothelin

Human Body Chemical Messengers
Interleukins (1, 4, 6, 33)
Nerve Growth Factor
Stem Cell Factor

Adapted from T. Theoharides

Allergen-IgE	Infections	Primary Immune Deficiency	Autoimmune Disorders
Avoidance measures (Diet, Environment) Medications: histamine blockade Desensitization (Immunotherapy) Omalizumab, Dupilumab Anti-interleukin mAb	Hepatitis, Lyme, Borrelia, EBV, HSV	Prophylactic Antibiotics Immune Globulin Anti-inflammatory Agents	Anti-inflammatory Agents Immune Globulin

Gratitude!



Patients and their families	Colleagues	Chiari Sryingomyelia Foundation
Ehlers Danlos Society	The Mastocytosis Society	Dysautonomia International

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