Mast Cell Activation Syndrome: The New Fibromyalgia?

introduction

what is MCAS?

diagnosis & treatment

pain & neuropsychiatric manifestations

key takeaways

Case

Artist credit: Kaitlin Walsh

Mast Cell Activation Syndrome – The New Fibromyalgia?

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FMF
Family Medicine Forum
Forum en médecine familiale

VANCOUVER CONVENTION CENTRE

THE COLLEGE OF FAMILY PHYSICIANS OF CANADA
LE COLLÈGE DES MÉDECINS DE FAMILLE DU CANADA

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Disclosures

Caveats

hypothesis

animals

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conflicts of interest
None to declare.
a note on medications
Off-label
a note on 'expertise'
A sprinkle of humility

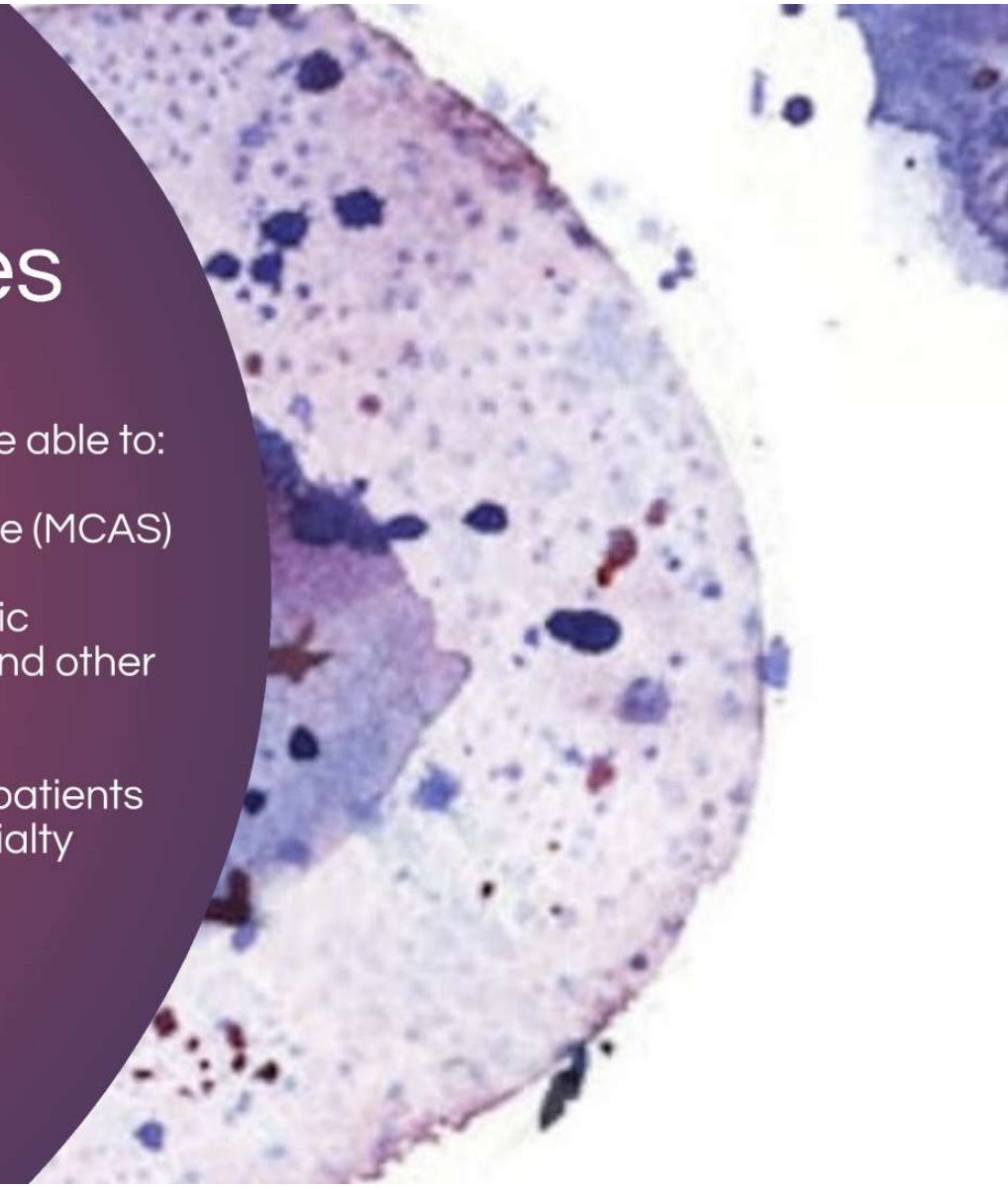
learning objectives

After this presentation, participants will be able to:

1. Describe Mast Cell Activation Syndrome (MCAS)

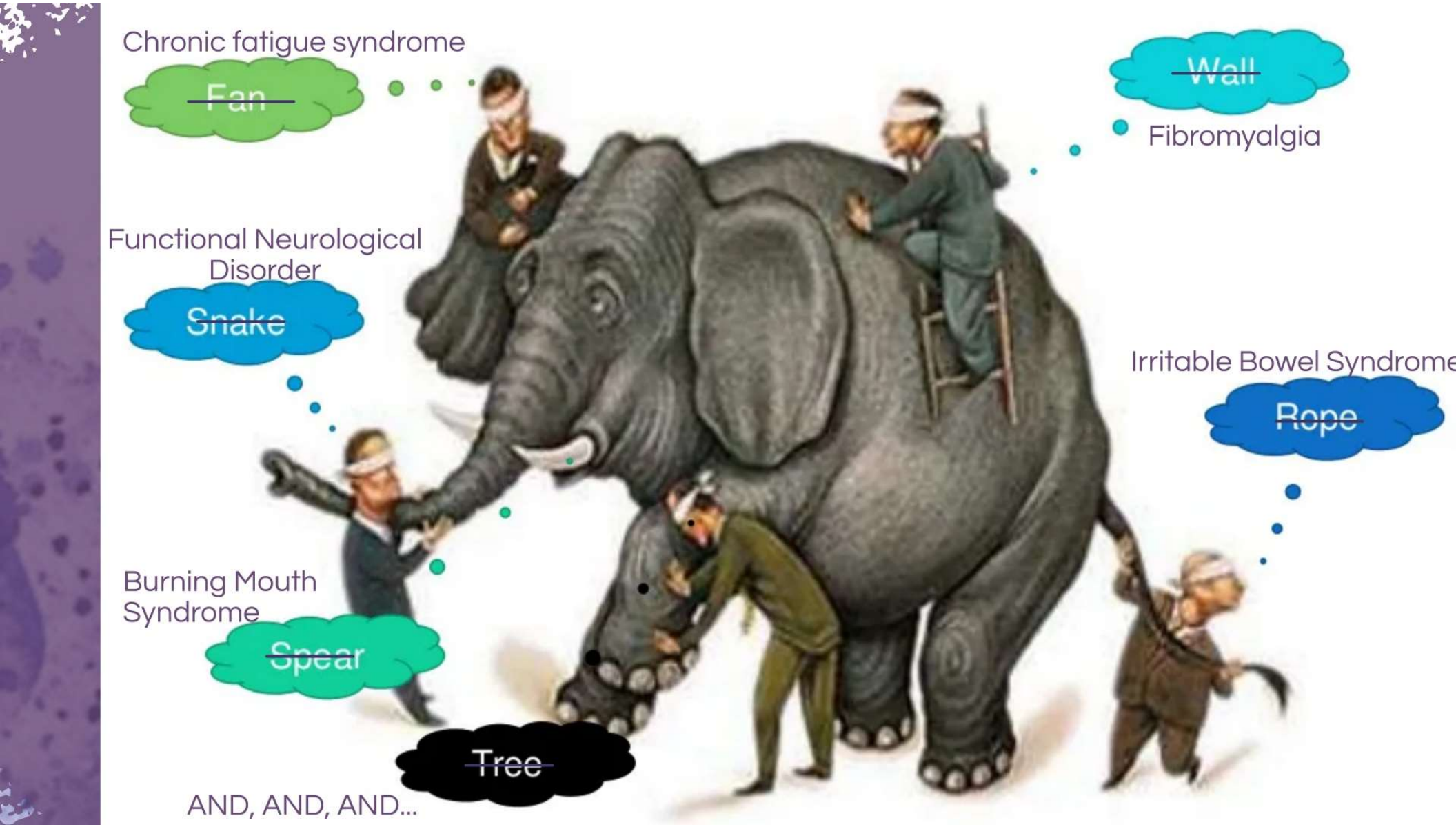
2. Implement a practical clinical diagnostic approach toward MCAS based on pain and other inflammatory symptoms

3. Initiate low-risk management for such patients while considering some patients for specialty consultation



6 Blind Men

fibromyalgia


Chronic fatigue syndrome
Fan
Wall
Fibromyalgia
Functional Neurological Disorder
Snake
Irritable Bowel Syndrome
Rope
Burning Mouth Syndrome
Spear
Tree
AND, AND, AND...

fibromyalgia symptoms

Symptom Severity Score (SS score)- Part 2b

Check each of the following OTHER SYMPTOMS that you have experienced over the <u>past week?</u>

- ☑ Muscle pain
- ☑ Irritable bowel syndrome
- ☑ Fatigue/tiredness
- ☑ Thinking or remembering problem
- ☐ Muscle Weakness
- ☑ Headache
- ☑ Pain/cramps in abdomen
- ☑ Numbness/tingling
- ☑ Dizziness
- ☑ Insomnia
- ☑ Depression
- ☑ Constipation
- ☑ Pain in upper abdomen
- ☑ Nausea
- ☑ Nervousness
- ☑ Chest pain
- ☑ Blurred vision
- ☑ Fever
- ☑ Diarrhea
- ☑ Dry mouth
- ☑ Itching
- ☑ Wheezing
- ☑ Raynauld's
- ☑ Hives/welts
- ☐ Ringing in ears
- ☑ Vomiting
- ☑ Heartburn
- ☑ Oral ulcers
- ☐ Loss/change in taste
- ☐ Seizures
- ☑ Dry eyes
- ☑ Shortness of breath
- ☑ Loss of appetite
- ☑ Rash
- ☑ Sun sensitivity
- ☐ Hearing difficulties
- ☑ Easy bruising
- ☑ Hair loss
- ☑ Frequent urination
- ☑ Painful urination
- ☑ Bladder spasms

TABLE 2. Most common (frequency ≥ 10%) symptoms in mast cell activation syndrome (MCAS). The denominator for each frequency is the eligible portion of the study population (e.g., fatigue: all patients [*N*= 413]; dysmenorrhea: only females [*N* = 287]).

Symptom	Frequency (%)	Symptom	Frequency (%)	Symptom	Frequency (%)
Fatigue	83	Palpitations/dysrhythmias	47	Poor healing	23
Fibromyalgia-type pain	75	Sweats	47	Sinusitis	17
Presyncope/syncope	71	Environmental allergies	40	Weight gain/obesity	17
Headache	63	Fever	40	Dental deterioration	17
Pruritus/urticaria	63	Nonanginal chest pain	40	Weight loss	16
Paresthesias	58	Easy bleeding/bruising	39	Cough	16
Nausea and vomiting	57	Alternating diarrhea/ constipation	36	Anxiety/panic	16
Chills	56	Proximal dysphagia	35	Multiple/odd drug reactions	16
Migratory edema	56	Insomnia	35	Dysmenorrhea	16
Eye irritation	53	Flushing ± diaphoresis	31	Asthma	15
Dyspnea	53	Visual anomalies	30	Alopecia	15
Gastroesophageal reflux	50	Oral irritation/sores	30	Constipation	14
Cognitive dysfunction	49	Adenopathy/adenitis	28	Depression	13
Rashes	49	Diarrhea	27	Tremor	13
Abdominal pain	48	Urinary sympt. excluding IC	27	Onychodystrophy	13
Throat irritation	48	Frequent or odd infections	27	Heat or cold intolerance or both	13

IC, interstitial cystitis.

Symptom Severity Score (SS score)- Part 2b

Check each of the following OTHER SYMPTOMS that you have experienced over the <u>past week?</u>

- ☑ Muscle pain
- ☑ Irritable bowel syndrome
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- ☑ Depression
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- ☑ Bladder spasms

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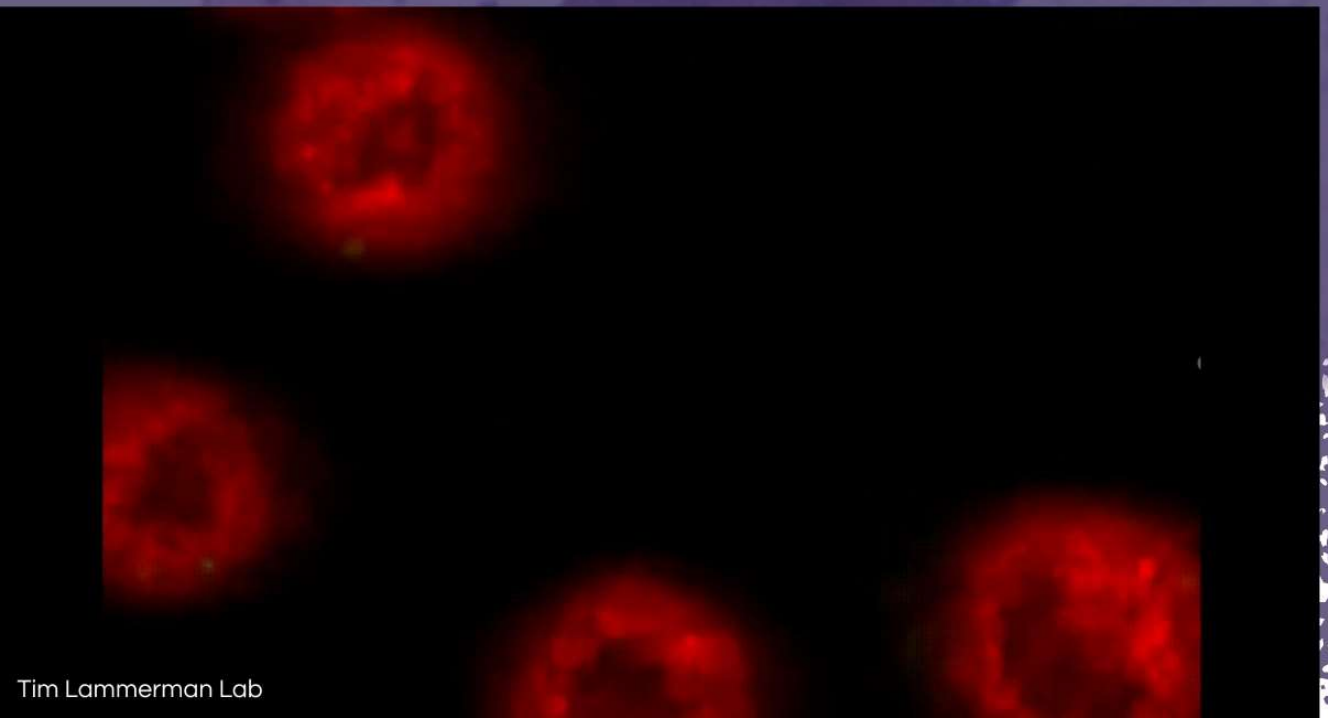
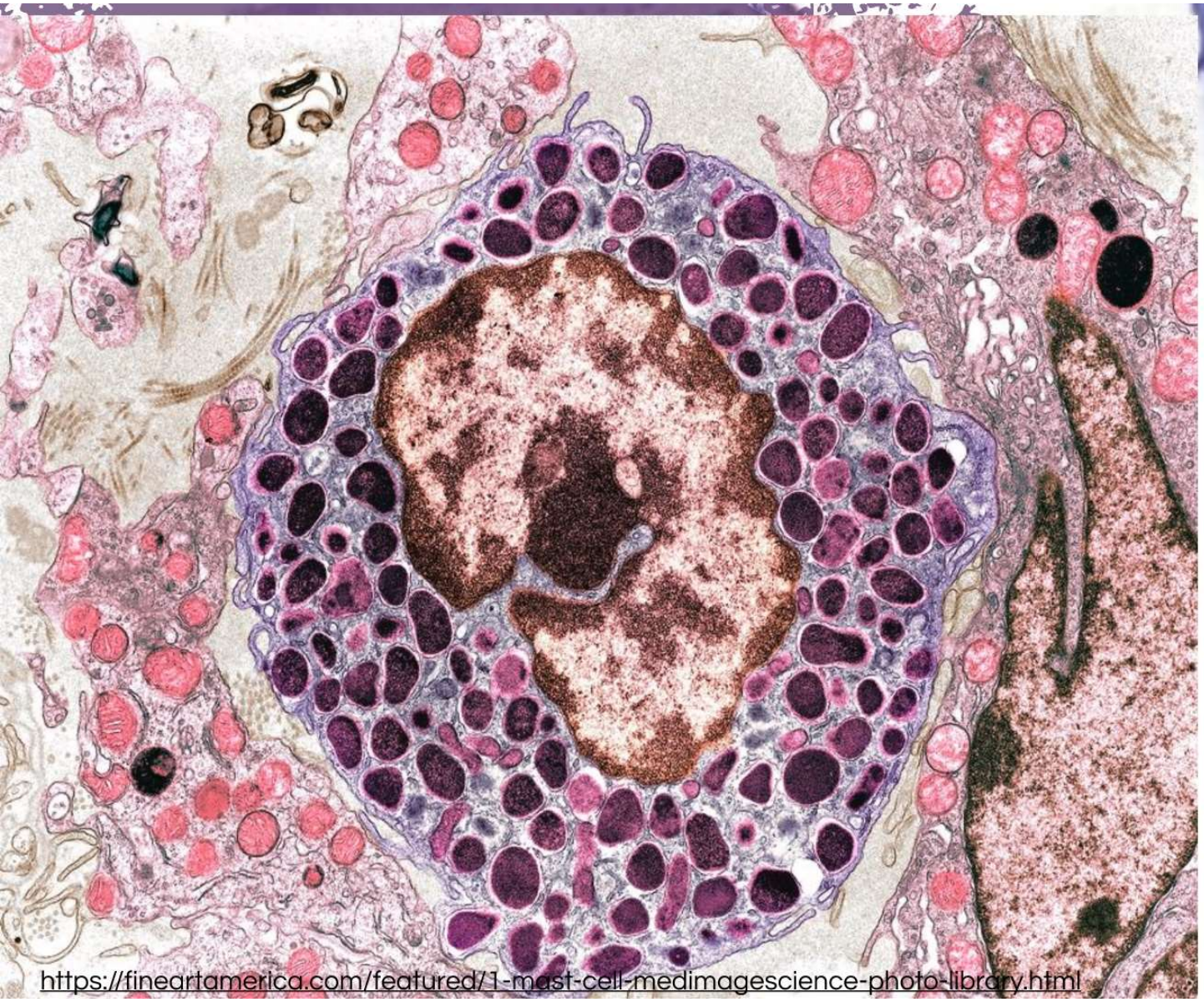
definition

chronic, inappropriate, non-neoplastic mast cell activation resulting in multisystem inflammatory ± allergic phenomena not fitting other defined allergic or inflammatory diseases

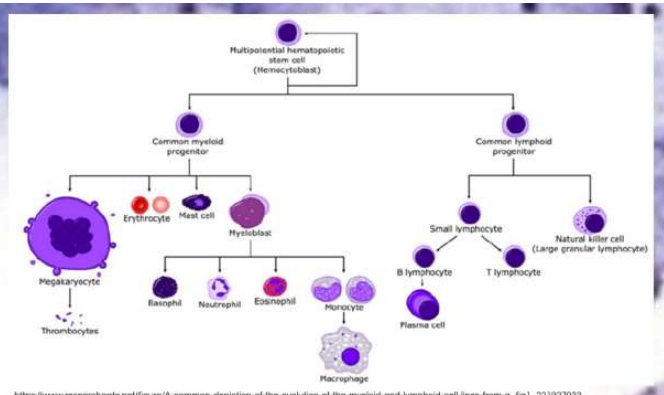


mast cells

patient characteristics



https://fineartamerica.com/featured/1-mast-cell-medimagescience-photo-library.html



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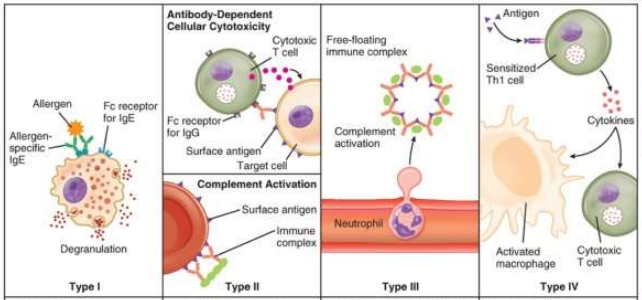
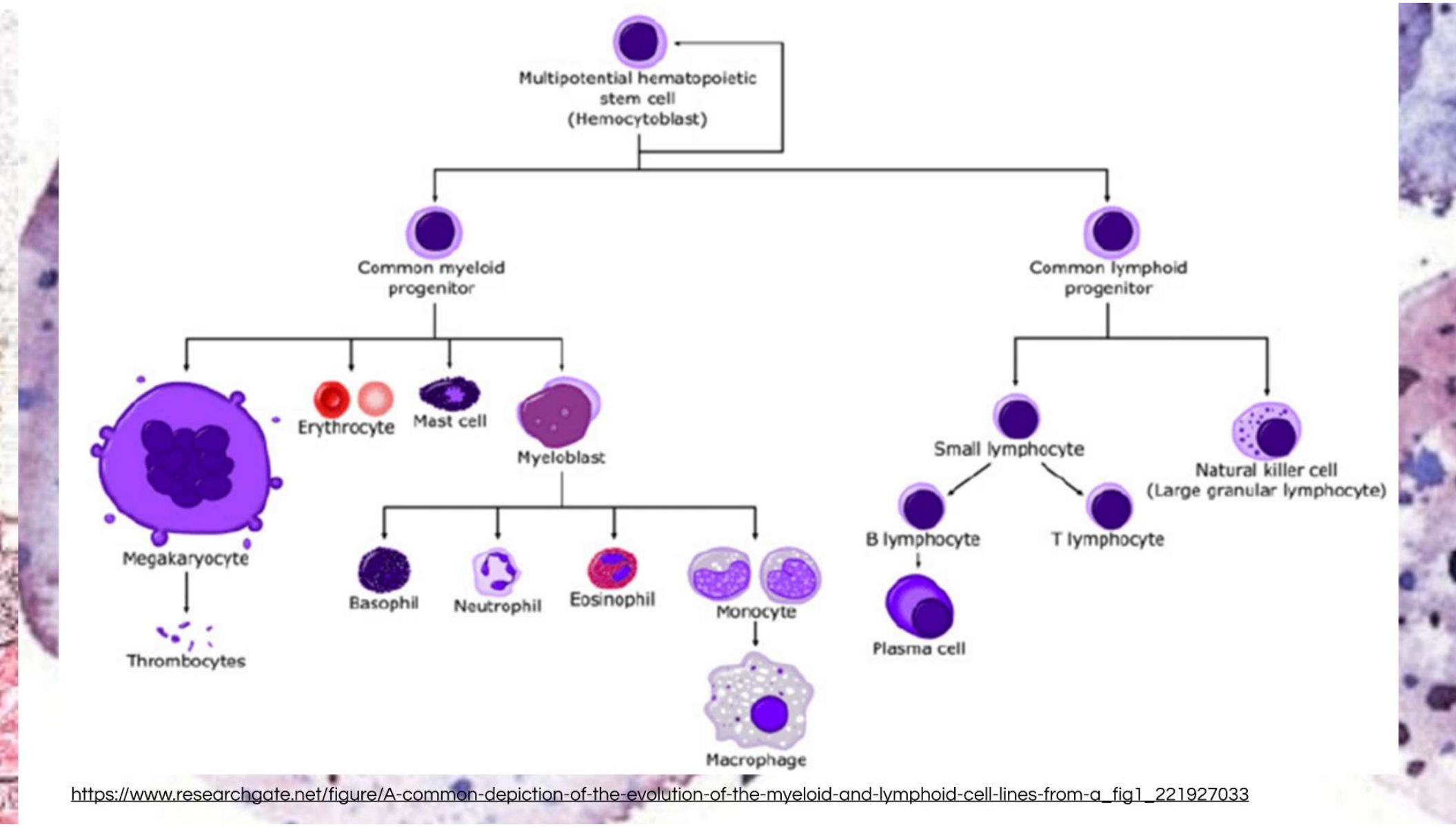


IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.	Cells are destroyed by bound antibody, either by activation of complement or by a cytotoxic T cell with an Fc receptor for the antibody (ADCC)	Antigen–antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site	Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site
Causes localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema	Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis	Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Most common forms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis

https://commons.wikimedia.org/wiki/File:2228_Immune_Hypersensitivity_new.jpg

Mediators

Fun Facts



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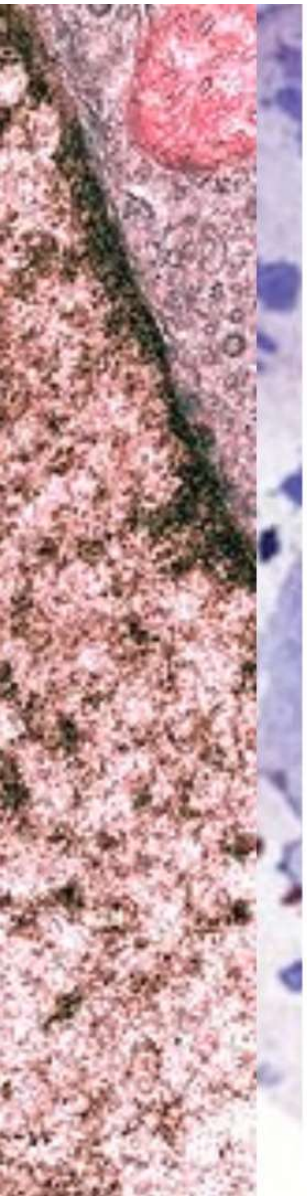
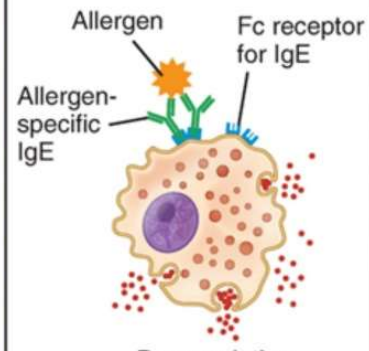
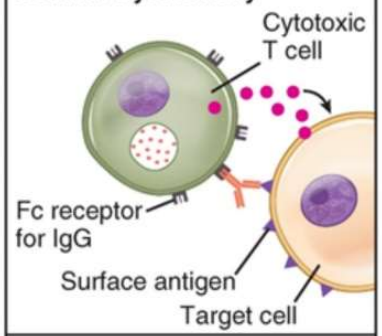
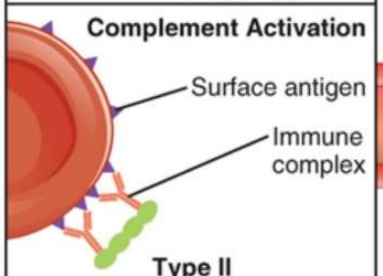
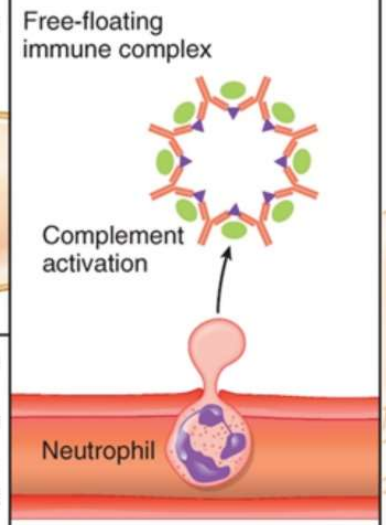
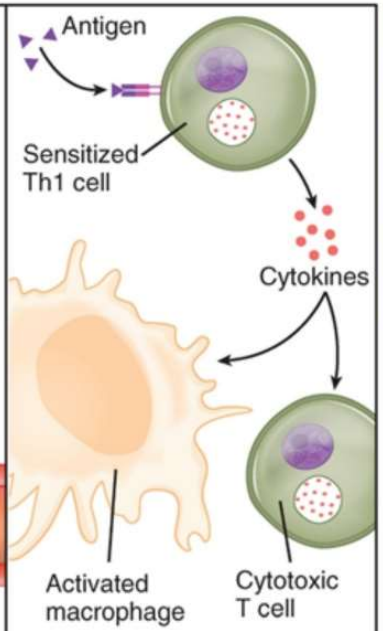


 **Type I**	  **Type II**	 **Type III**	 **Type IV**
IgE-Mediated Hypersensitivity	**IgG-Mediated Cytotoxic Hypersensitivity**	**Immune Complex-Mediated Hypersensitivity**	**Cell-Mediated Hypersensitivity**
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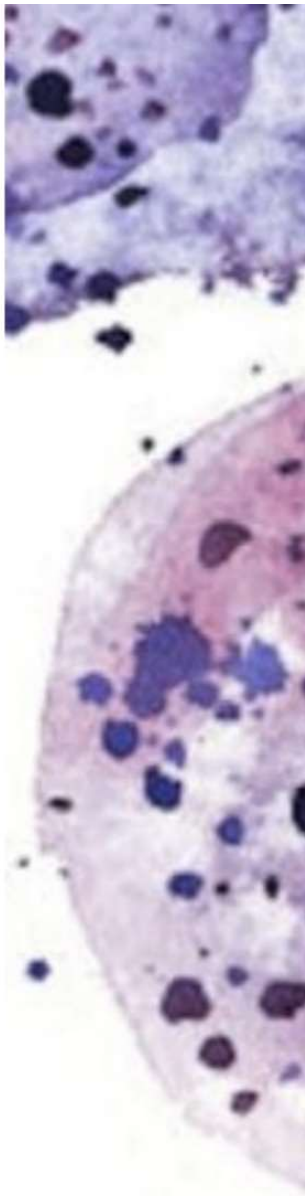
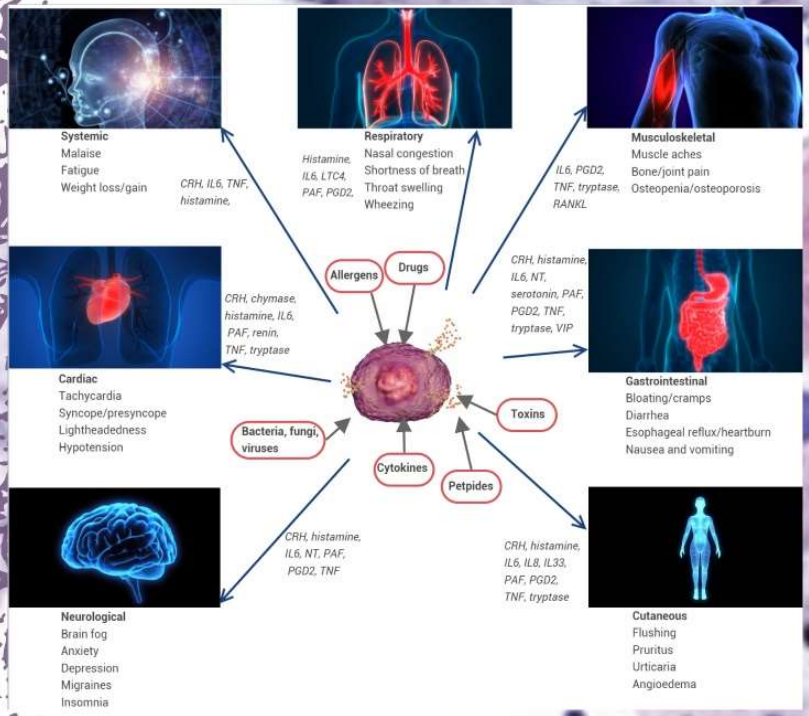


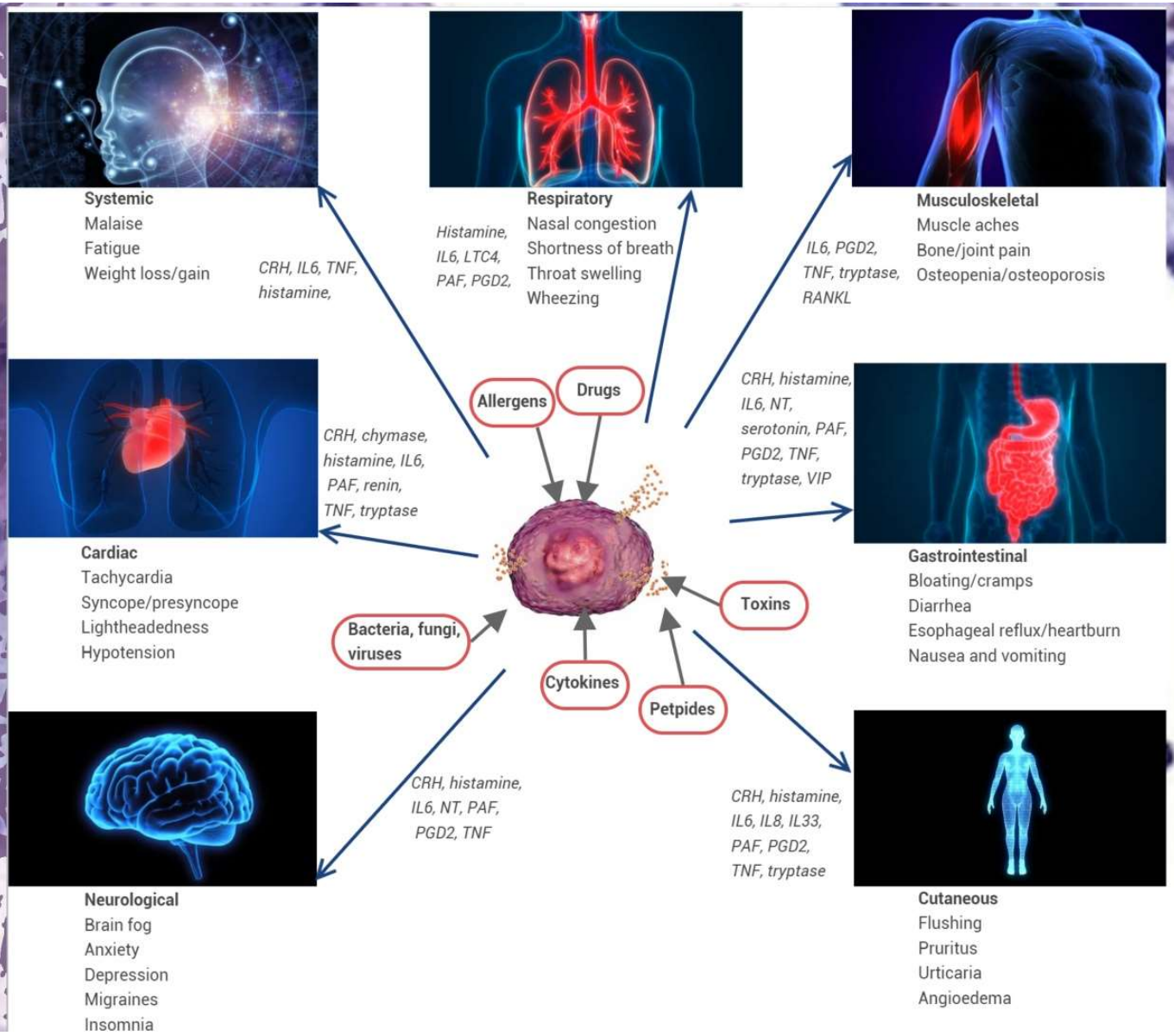
Mediators

- Histamine
- Platelet activating factor
- Prostaglandin D2
- Leukotriene C4
- Tumour necrosis factor
- Chromogranin A
- Tryptase (elevated in anaphylaxis and mastocytosis)
- Heparin (elevated in 80% of MCAS patients)
- and 1050+ other chemicals!

COPE (Cytokines and Cells Online Pathfinder Encyclopedia) Library:
http://www.cells-talk.com/version_act/images/download/MAST-CELLS-SAMPLE_ENTRY.pdf

- Lives in tissue, not the blood stream
- Common progenitor, but differentiates based on the tissue
- Affinity for borders with the outside world
  - Skin
  - GI
  - Lungs
- Some mediators released immediately
  - 5-30 seconds
- Other release over hours
- Mast cells can release mediators selectively
- Mast cells have impact on every system

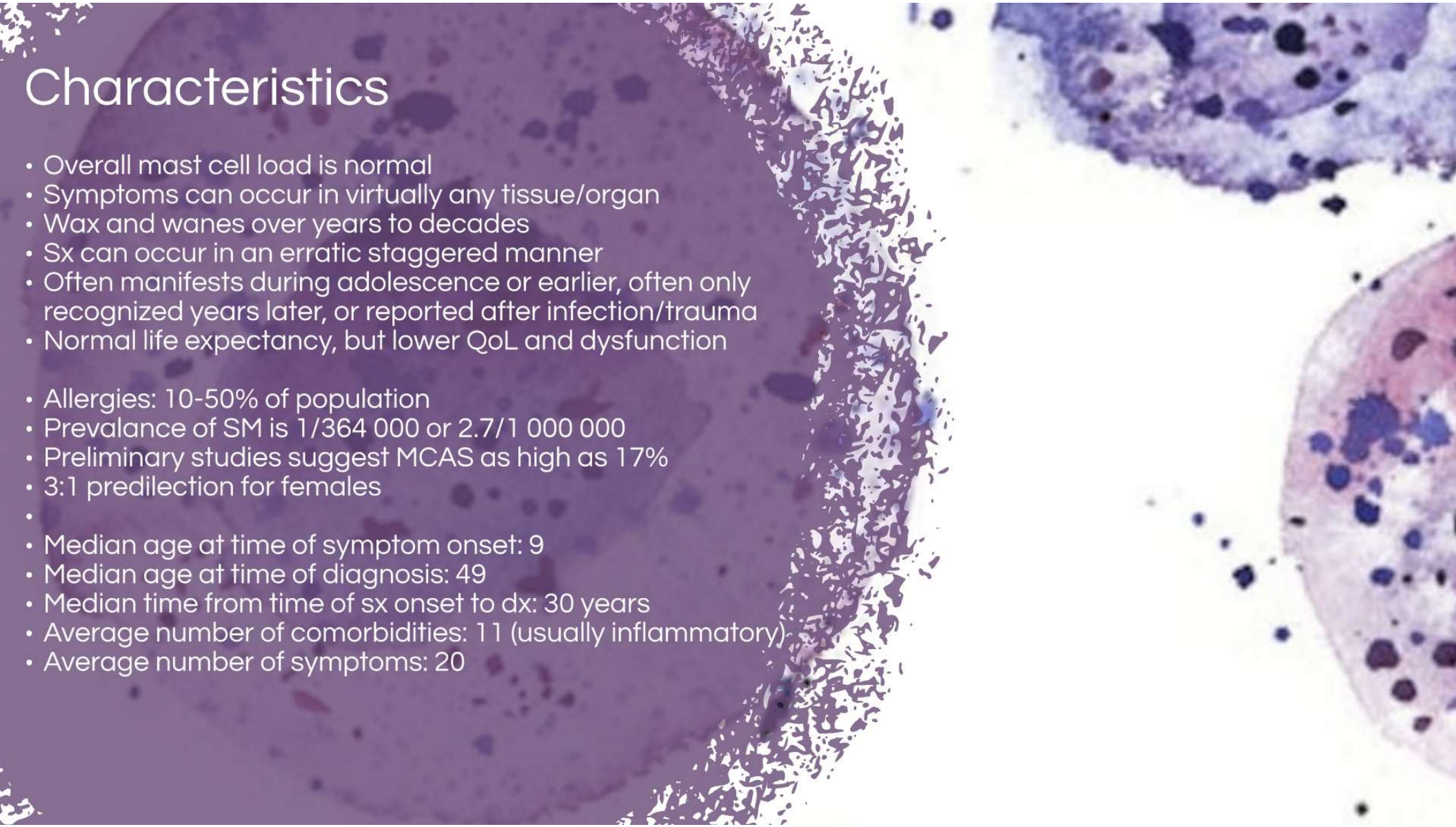



Systemic
Malaise
Fatigue
Weight loss/gain
CRH, IL6, TNF, histamine,
Respiratory
Nasal congestion
Shortness of breath
Throat swelling
Wheezing
Histamine, IL6, LTC4, PAF, PGD2,
Musculoskeletal
Muscle aches
Bone/joint pain
Osteopenia/osteoporosis
IL6, PGD2, TNF, tryptase, RANKL
Allergens
Drugs
CRH, chymase, histamine, IL6, PAF, renin, TNF, tryptase
Cardiac
Tachycardia
Syncope/presyncope
Lightheadedness
Hypotension
CRH, histamine, IL6, NT, serotonin, PAF, PGD2, TNF, tryptase, VIP
Gastrointestinal
Bloating/cramps
Diarrhea
Esophageal reflux/heartburn
Nausea and vomiting
Toxins
Bacteria, fungi, viruses
Cytokines
Petpides
CRH, histamine, IL6, NT, PAF, PGD2, TNF
Neurological
Brain fog
Anxiety
Depression
Migraines
Insomnia
CRH, histamine, IL6, IL8, IL33, PAF, PGD2, TNF, tryptase
Cutaneous
Flushing
Pruritus
Urticaria
Angioedema

Characteristics

- Overall mast cell load is normal
- Symptoms can occur in virtually any tissue/organ
- Wax and wanes over years to decades
- Sx can occur in an erratic staggered manner
- Often manifests during adolescence or earlier, often only recognized years later, or reported after infection/trauma
- Normal life expectancy, but lower QoL and dysfunction

- Allergies: 10-50% of population
- Prevalance of SM is 1/364 000 or 2.7/1 000 000
- Preliminary studies suggest MCAS as high as 17%
- 3:1 predilection for females
-
- Median age at time of symptom onset: 9
- Median age at time of diagnosis: 49
- Median time from time of sx onset to dx: 30 years
- Average number of comorbidities: 11 (usually inflammatory)
- Average number of symptoms: 20



consensus 1 and consensus 2

Valent Criteria

3 criteria must be fulfilled:

1. Episodic occurrence of typical mast cell-related sx
   - Hives, swelling, flushing, itching
   - N&V, cramps, diarrhea
   - Headache, conjunctival injection, nasal congestion, hoarse voice
   - Palpitations, lightheadedness
   - Two or more organ systems should be involved

2. Significant elevation of tryptase by 20% + 2ng/ml within 4 hrs after a flare

3. Response to sx by drugs targeting mast cell mediators (H1 or H2 blockers, montelukast) or mast cell stabilizers (cromolyn, ketotifen, omalizumab) or combinations

Diagnosis of MCAS: A global "consensus 2": https://pubmed.ncbi.nlm.nih.gov/32324159/
*Make sure to take a look at Supplementary Material

Molderings Criteria

Proposed criteria defining Mast Cell Activation Syndrome (MCAS) (52)

Major criteria

1. Multifocal or disseminated dense infiltrates of MCs in marrow and/or extracutaneous organ(s) (e.g., gastrointestinal or genitourinary tract)
2. Constellation of clinical complaints attributable to pathologically increased MC activity (MC mediator release syndrome)

Minor criteria

1. Abnormal spindle-shaped morphology in >25% of MCs in marrow or other extracutaneous organ(s)
2. Abnormal MC expression of CD2 and/or CD25 (i.e., co-expression of CD117/CD25 or CD117/CD2)
3. MC genetic changes (e.g., activating KIT codon 816 mutations) shown to increase MC activity
4. Evidence (typically from body fluids such as whole blood, serum, plasma, or urine) of above-normal levels of MC mediators including:
   - Tryptase
   - Histamine or its metabolites (e.g., *N*-methylhistamine)
   - Heparin
   - Chromogranin A (note potential confounders of cardiac or renal failure, neuroendocrine tumors, or recent proton pump inhibitor use)
   - Other relatively MC-specific mediators (e.g., eicosanoids including prostaglandin (PG) D_2, its metabolite 11-β-$PGF_{2\alpha}$, or leukotriene E4)
5. Symptomatic response to inhibitors of MC activation or MC mediator production or action

MCAS Validated Questionnaire

Clinical Signs & Symptoms

The patient shows involvement of the skin in terms of:

- ☐2 Brown-reddish maculopapular rash/eruption.
- ☐2 Angioedema of the lips, lids of the eye, infraorbital.
- ☐1 Pruritus without rash/eruption and/or disease-related folliculitis.
- ☐1 A clear increase in the number of telangiectasias.

☐1 The patient reports sudden attacks of migraine-like headaches.

☐1 The patient reports memory loss (ability to remember names or words) and/or concentration difficulty and/or sleep disturbances.

☐1 The patient reports tinnitus attacks and/or ocular discomfort (dry eyes, red eyes, stinging eyes) and/or rhinorrhea/chronic nasal congestion and/or stomatitis (score if two or more of these symptoms are present).

☐1 The patient reports non-allergic respiratory ailments such as asthma, compulsion to clear the throat, titillating/ticklish feeling in the respiratory tract and/or shortness of breath during routine tasks.

☐1 In the past, common viral upper respiratory tract infections were frequently complicated by bacterial superinfection.

☐1 The patient can state precisely the date of the first clinical manifestation of the mast cell mediator release syndrome because it appears to him/her to be associated with an infectious disease.

☐1 The patient complains about recurring or continuing burning and/or crampy abdominal pain of unknown cause and/or recurring or continuing diarrhea of unknown cause and/or frequently intense meteorism/gassiness (independent of the composition of diet) and/or about episodically occurring nausea.

☐1 The symptoms respond to treatment with H1-antihistamines.

☐1 The progression of the symptoms occurred in episodes with symptom-free periods becoming shorter.

☐1 The patient complains about episodically occurring burning and/or choking chest pain attacks, which are often experienced as life-threatening. Electrocardiographic findings are without pathological signs.

☐1 The patient complains about occasional or continuing pain in the urinary bladder and/or pelvis accompanied by painful desire to void and/or blood in the urine. There is no bacteriuria.

☐1 The patient complains about occasional or continuing paresthesia (burning, pins and needles, numbness) and/or pain which does not respond to treatment with analgesics.

☐1 During symptomatic periods of the disorder the patient is afflicted with anal pruritus and/or anal eczema.

The patient reports the following signs of episodically occurring symptoms of autonomic dysfunction:

- ☐1 Tachycardia or palpitation/dysrhythmia
- ☐2 Flushing (redness, feeling of heat),
- ☐2 Hot flash, sweats
- ☐2 Paroxysmal hypo/hypertension with dizziness to the point of syncope

☐1 The patient shows signs of a bleeding diathesis (ex. abnormal secondary bleeding/bruising after minimal trauma and/or lesions).

Triggering Factors

☐1 Deprivation of sleep

☐1 Fasting for 24h

☐1 Histamine containing food (ex. red wine, cheese, tuna)

Laboratory Parameters

Despite no pathological findings in routine laboratory parameters and imaging methods, the patient presents with a pronounced:

- ☐1 Asthenia.
- ☐1 Fatigue.
- ☐1 Loss in weight.

☐1 During symptomatic periods of the disorder the patient showed, at least once, hyperbilirubinemia (up to 2.5mg/dL or 42.8mmol/L), and/or an increase of transamidases (up to twice their upper limits of normal) and/or diet-independent hypercholesterolemia (up to 300mg/dL or 7.8mmol/L).

☐1 There are low titres of autoantibodies without clinical signs in the organs or tissues against which the autoantibodies are directed.

The serum total tryptase was:

- ☐0 Normal.
- ☐3 Elevated >11 and <20ng/ml.
- ☐10 Elevated more than 20ng/mL.

☐3 The level of chilled plasma heparin in blood was elevated >0.05 anti-Factor Xa units/mL.

The level of chilled N-methylhistamine in a 24-hour urine collection was:

- ☐1 Marginally elevated.
- ☐5 Elevated up to tenfold of the reference value.
- ☐10 Elevated by more than tenfold of the reference value.

Pathology Findings

Gastroscopy and biopsies from the stomach and duodenum:

- ☐1 Show minor signs of inflammation.
- ☐3 Show Helicobacter pylori- and NSAID-negative erosions and/or ulcers.
- ☐10 Show clusters of mast cells (requires CD117 staining) and/or a considerable number of spindle-shaped mast cells and/or CD25-positive mast cells.

Colonoscopy and intestinal biopsies:

- ☐1 Show minor signs of inflammation.
- ☐1 Show melanosis coli (abuse of anthra-cenediones ruled out).
- ☐10 Show clusters of mast cells (requires CD117 staining) and/or a considerable number of spindle-shaped mast cells and/or CD25-positive mast cells.

Imaging

☐1 The patient has splenomegaly and/or hepatomegaly.

☐1 The patient has bone pain with signs of osteoporosis and/or osteopenia and/or osteosclerosis.

☐1 Intestinal adhesions are present without prior history of abdominal surgery.

A total score > 8 but <14 indicates a pathological activation of mast cells. A total score of ≥14, a systemic mast cell mediator release syndrome is clinically verified.

Afrin, L. B., Butterfield, J. H., Raithel, M., & Molderings, G. J. (2016). Often seen, rarely recognized: Mast cell activation disease – a guide to diagnosis and therapeutic options. *Annals of Medicine, 48*(3), 190-201. doi:10.3109/07853890.2016.1161231

Alfter, K., von Kügelgen, I., Haenisch, B., Frieling, T., Hülsdonk, A., Haars, U., . . . Molderings, G. J. (2009). New aspects of liver abnormalities as part of the systemic mast cell activation syndrome. *Liver International : Official Journal of the International Association for the Study of the Liver, 29*(2), 181-186. doi:10.1111/j.1478-3231.2008.01839.x [doi]

Molderings, G. J., Kolck, U., Scheurlen, C., Brüss, M., Frieling, T., Raithel, M., & Homann, J. (2006). Systemic mast cell disease with gastrointestinal symptoms--a diagnostic questionnaire. [Die systemische Mastzellerkrankung mit gastrointestinal betonter Symptomatik--eine Checkliste als Diagnoseinstrument] *Deutsche Medizinische Wochenschrift (1946), 131*(38), 2095-2100. doi:10.1055/s-2006-951337 [doi]

Patient Version

DDx

https://www.humangenetics.uni-bonn.de/de/forschung/forschungsprojekte/mastzellerkrankungen/validatedquestionnaire

Mast Cell Mediator Release Syndrome Questionnaire

Answer all of the following questions about symptoms, even if they are only slightly bothersome, rarely occurring, or have occurred in the past, even if it does not seem related to your health concerns.
Check the box if the statement applies to you.

Constitutional

☐1 Significant physical weakness of fatigue doing everyday activities.
☐1 Extreme fatigue attacks, and difficulty keeping my eyes open.
☐1 At times I lose weight despite maintaining my normal diet.
Complaints of any kind (including others below) are worsened by:
☐1 Sleep deprivation (awake for more than 24 hours)
☐1 Hunger or fasting (no food all day)
☐1 High histamine foods (such as red wine, cheese, chocolate, tuna, cure fish/meat, left-over meat)
☐0 Alcohol consumption
☐0 Physical exertion
☐0 Heat
☐0 Cold
☐0 Stress

Eyes/Ears/Nose/Mouth

☐1 Score if one or more symptom is present:
Ears have ringing or odd sound and/or
Eyes are dry, itchy, red, burning, or feel gritty and/or
Chronically runny nose or stuffy nose and/or
Inflammation or ulcers of the mouth

Chest and Heart

The following occurs repeatedly or may be constant:
☐1 Burning and/or pressure pain in the chest and heart tests were normal (electrocardiogram and/or stress test)
☐1 Rapid heart rate or frequent skipped beats (palpitations)
☐2 Redness or flushing of the skin, especially of the face or upper body
☐2 Hot flashes (usually lasting 2-5 minutes, rarely up to 10 minutes and often accompanied by nausea or other symptosm; not hot flashes of menopause)
☐2 Sudden dizziness/lightheadedness with fainting or near faint or sudden temporary increase/decrease in blood pressure
☐0 I have seen evidence for pulse and blood pressure changes using my digital watch device

Lungs

The following occurs repeatedly or may be constant:
☐1 Irritable dry cough or need to cough and/or feeling or shortness of breath or difficulty taking a full breath and/or asthma-like complaints (wheezing)

Abdomen

The following occurs repeatedly or may be constant:
☐1 Nausea (with or without vomiting), and/or pain in the abdomen, and/or character of the pain is burning or crampy or spastic, and/or associated with diarrhea, and/or with attacks of visible bloating or distension within minutes (up to around 10 minutes)
☐1 A surgeon told me that adhesions (scar tissue) were seen during my very first laparoscopy or abdominal/pelvic surgery

Urine/Pelvis

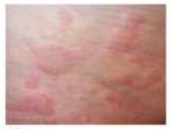
The following occurs repeatedly or may be constant:
☐1 Bladder and/or pelvic pain (both women and men) and is often associated with painful, frequent and/or urgent urination, may be associated with pain during sex; during these times bacterial cultures and urine analysis are normal
☐0 I have had these symptoms but have not seen a doctor to order tests.

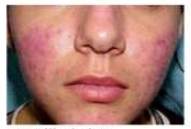
Neurologic

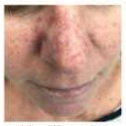
The following occurs repeatedly or may be constant:
☐1 Headaches (may be throbbing on one side only or have previously been diagnosed as a migraine)
☐1 Brain fog – word finding problems and/or concentration difficulties with or without associated insomnia episodes.
☐1 Neuropathy – leg pain or arm pain and/or altered feelings of numbness, tingling, or pins and needles which does not respond to most pain medications.

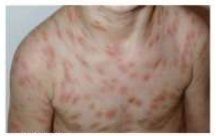
Skin – see photos for examples

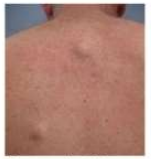
The following occurs repeatedly or may be constant:
☐1 Hives (red raised itchy spots)
☐1 Itching with or without skin changes
☐1 Itchy skin lesions that look like acne in the cornes of the nasal or lip area, chin, or forehead during attacks
☐1 Itching around the anus during attacks
☐1 Painless, non-itchy swelling (especially lips, cheeks, eyelids)
☐2 Reddish-brown spots and/or knots under the skin
☐1 Hemangiomas (‘blood sponges’)

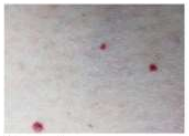

Hives


Acne-like lesions


Spider-like veins


Reddish-brown spots


Knots under skin


Hemangiomas

Hematologic

The following occurs repeatedly or may be constant:
☐1 Bruising after minor injuries and/or unusual nose bleeds and/or in women, significantly increased menstrual bleeding

Bone

☐1 Bone pain that usually occurs in more than one bone
☐1 Bone density test showed osteoporosis or osteopenia and/or whole-body nuclear scintigraphy showed areas of increased bone metabolism without a known cause

General Questions

☐1 Do you get colds regularly which then turn into bacterial infections such as bronchitis or sinus infections?
☐1 Do your symptoms occur in episodes or as an attack?
☐1 Have symptom-free periods become shorter?
☐1 Any degree of relief of symptoms by taking antihistamines (such as diphenhydramine, loratadine, ranitidine, famotidine, cetirizine)?
☐1 Do you know with relative certainty the beginning of your symptoms are linked to a memorable event such as infection, stress, environmental change, etc)?

9-13 Symptoms consistent with probable mast cell activation
≥14 **Symptoms consistent with mast cell activation syndrome**

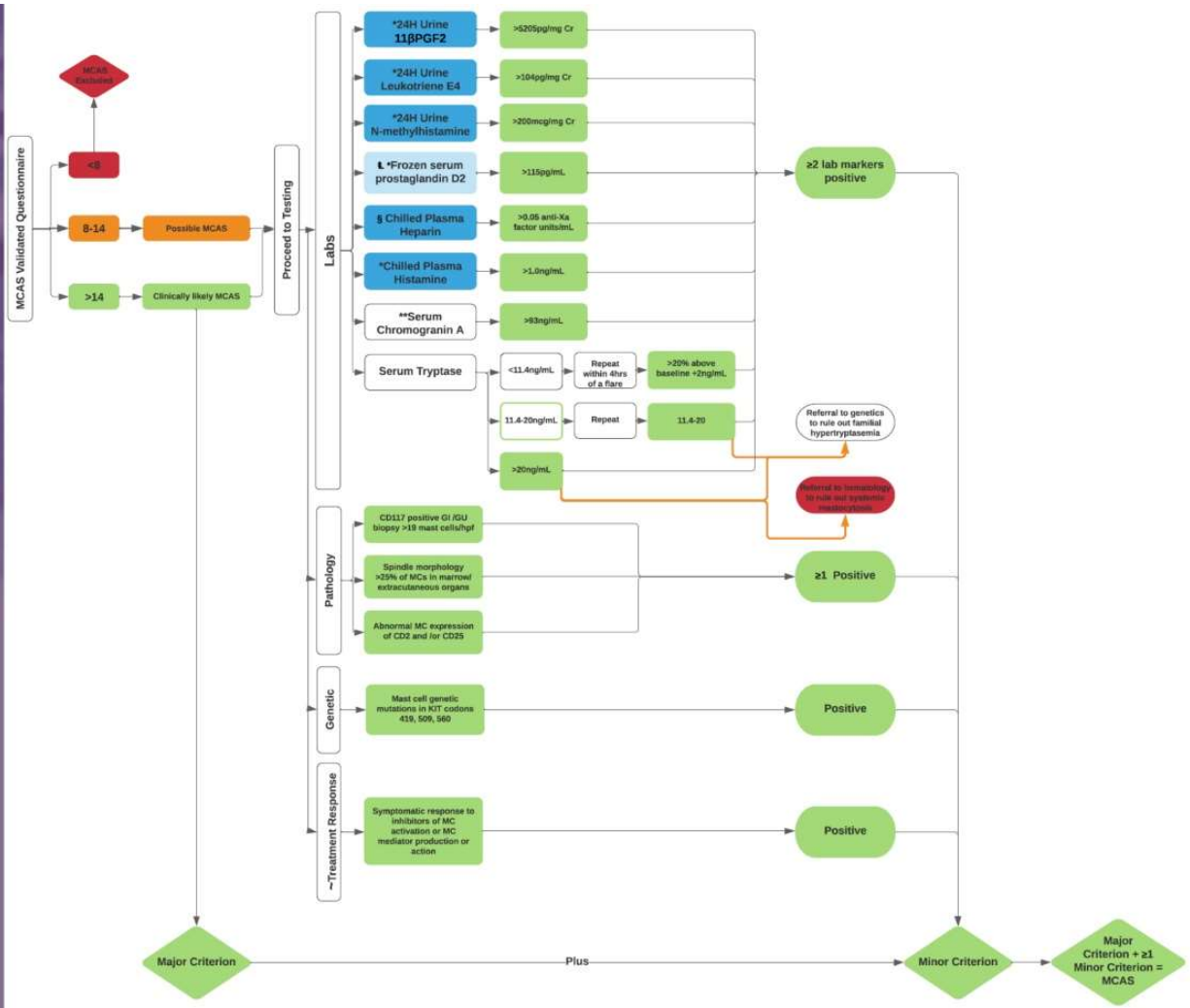
DIFFERENTIAL DIAGNOSIS (and testing for disorder that may have similar symptoms as mast cell activation)

ENDOCRINE
Diabetes mellitus (laboratory determination)
Porphyria (laboratory determination)
Hereditary hyperbilirubinemia (genetic testing)
Thyroid disorders (laboratory determination)
Fabry disease (clinical picture, genetic examination)

GASTROINTESTINAL
Helicobacter-positive gastritis (gastroscopy, biopsy, urea breath test, fecal antigen)
Infectious enteritis (stool examination)
Parasitoses (examination)
Inflammatory bowel disease (endoscopy, biopsy)
Celiac disease (laboratory determination, biopsy)
Lactose, sucrose, or fructose intolerance as an independent disease (history, breath tests)
Microscopic colitis (endoscopy, biopsy)
Amyloidosis (fat biopsy, rectal biopsy)
Adhesions, volvulus, and other intestinal obstructions (history, physical, imaging studies)
Hepatitis (laboratory determination)
Cholecystitis (imaging studies)
Median arcuate ligament syndrome (auscultation, CT angiography with deep expiration views)

IMMUNOLOGICAL AND NEOPLASTIC DISEASES
Carcinoid tumor (laboratory determination, octreotide imaging)
Pheochromocytoma (laboratory determination)
Pancreatic endocrine tumors [gastrinoma, insulinoma, glucagonoma, somatostatin, VIPoma] (Lab determination, imaging studies, endoscopic ultrasound)
Food allergy/sensitivity (history, special investigations of the biopsies, elimination diet)
Hypereosinophilic syndrome (laboratory determination)
Hereditary angioedema (family history, laboratory determination)
Vasculitis (clinical picture, laboratory value determination)
Intestinal lymphomas (imaging studies)

putting it all together. . .



*Not available in most provinces, requires special forms for Mayo Clinical Laboratories.
**Hold proton pump inhibitors for 5+ days prior to testing for CgA; R/O neuroendocrine/carcinoid tumour, cardiac failure, renal failure.
Boxes in blue, refrigerate or freeze as directed for entire testing chain due to significant thermolability of mediator being tested.
ʟ Hold NSAIDs 5 days before testing.
§ For patients not on exogenous heparin products; requires ultra-sensitive assay to 0.02 units/mL.
~Treatment response can be considered in rural/remote areas or in low resource settings.

Mast Cell Activation Syndrome: Antihistamine Trial Instructions

Start one medication at a time at the lowest dose, observing for reactions or side effects, and if tolerated increase to the maximum doses instructed within a few days. If after 2 weeks you have not noted any significant benefits, stop taking it and move on to the next. Most MCAS patients find that one particular anti-histamine is more effective than others.

Note that H1 and H2 antihistamines can be taken at the same time. So, if you find that you have found an H1 antihistamine that helps, you can trial H2 antihistamines one a time while continuing to take the H1 antihistamine.

H1 Antihistamines – usually more helpful for widespread pain symptoms including burning, itching

Generic	Brand Name	Dosing instructions	Prescription Required
Loratadine	Claritin	10mg daily, increase to 20mg twice daily	No
Cetirizine	Reactin	10mg daily, increase to 20mg twice daily	No
Desloratadine	Aerius	5mg daily, increase to 10mg twice daily	No
Fexofenadine	Allegra	60mg daily, can take 60mg three times daily, or 180mgonce daily	No
Bilastine	Blexten	20mg daily, up to 40mg twice daily	Yes
Rupatadine	Rupall	10mg daily, up 20mg once daily	Yes
Diphenhydramine	Benadryl	25-50mg every 6 hours	No

H2 Antihistamines – usually more helpful for gastrointestinal symptoms

Generic	Brand Name	Dosing instructions	Prescription Required
Famotidine	Pepcid	20mg daily, increase to 20mg twice daily	No
Ranitidine	Zantac	150mg twice daily	No
Cimetidine	Cimetidine	200mg twice daily	Yes
Nizatadine	Axid	150mg twice daily	Yes

Supplements:

Mast cell stabilizer: slow-release vitamin C 1000mg twice daily
Quercetin 250mg to 1000mg twice daily
Luteolin 100-400mg twice daily (available from the US)

Antihistamines with unique indications:

Generic	Brand Name	Dosing instructions	Prescription Required
Meclizine (H1)		12.5-25mg every 6-8 hours as needed, max 100mg/day *(for short-term vertigo management up to 3 days; for motion sickness)*	No
Cyproheptadine (H1)		2mg 4x/day before meals, max 16mg/day *(for functional abdominal pain, poor appetite, cyclical vomiting syndrome, migraine prophylaxis)*	No
Cimetidine (H2)		200mg 2-3 times daily, max 800mg/day *(for interstitial cystitis)*	Yes
Hydroxyzine (H1)	Atarax	25-100mg per dose, up to 4x/day, max 400mg/day *(for urticarial, and anxiety)*	Yes
Doxepin (H1 and H2)	Silenor	10mg at night *(for insomnia, and off-label for urticaria)*	Yes
Mirtazipine (H1)	Remeron	7.5-15mg at night *(for insomnia, less antihistaminergic effects at doses higher than this)*	Yes

Topical

Olopatadine	Pazeo, Patanol, Pataday	Eye drops and as a nasal spray	No
Ketotifen	Zatidor	Eye drops	Yes
Cromolyn		4% eye drops	No
Bepotastine	Bepreve	Eye drops	Yes
Azelastine	Dymista	Nasal spray combined with steroid, consider with ++ facial symptoms	Yes
Diphenhydramine	Benadryl	2% topical cream	No

OTC Consider with caution in suggesting for short-term use

Brompheniramine	Dimetapp	Combo product 2mg with 5mg phenylephrine, long-term use not suggested due to cardiovascular risks associated with phenylephrine	No

Mast Cell Stabilizers

Ketotifen	Zatiden	1mg twice daily, titrate up to 4mg twice daily	Yes
Cromolyn	Nalcrom	200mg prior to meals, up to 4 times daily	Yes

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treatment principles

1. Avoid Triggers
2. Specific mediator antagonists:
   - H1 and H2 blockers
   - Leukotriene antagonists (montelukast)
   - Cyclo-oxygenase inhibitors (ASA, Celebrex)
3. Mast cell stabilizers
   - Sodium cromoglicate
   - Ketotifen
4. Low-dose naltrexone
5. Tyrosine kinase inhibitors
   - Imatinib
6. Anti-IgE monoclonal antibodies
   - Omalizumab
7. Supplements
   - Slow-release vitamin C
   - Quercetin
   - Luteolin

Used in combination

Neuropsychiatric Symptoms

pain
brain fog
orthostatic intolerance
cognitive dysfunction
anxiety/panic/PTSD
ADHD
autism
small fiber neuropathy
fibromyalgia
migraines

Novak et al. 2021, Ann. Asthma Allergy Immunol.

Afrin et. al 2016, Ann. Med.

Neurologic	Headache (especially migraine) (63%), presyncope and/or syncope, peripheral (usually distal) sensory and/or motor neuropathies including paresthesias (58%), tics, tremors (13%; typically resting), chronic inflammatory demyelinating polyneuropathy, seizure disorders (can be "treatment-refractory")
Psychiatric	Mood disturbances (e.g., anger, depression (13%)), bipolar affective disorder, attention deficit-hyperactivity disorder, post-traumatic stress disorder, other anxiety and panic disorders (16%), psychoses, memory and concentration and word-finding difficulties and other cognitive dysfunction (49%), wide variety of sleep disruptions (including insomnia (35%) and obstructive sleep apnea regardless of weight)

mast cells and nociception

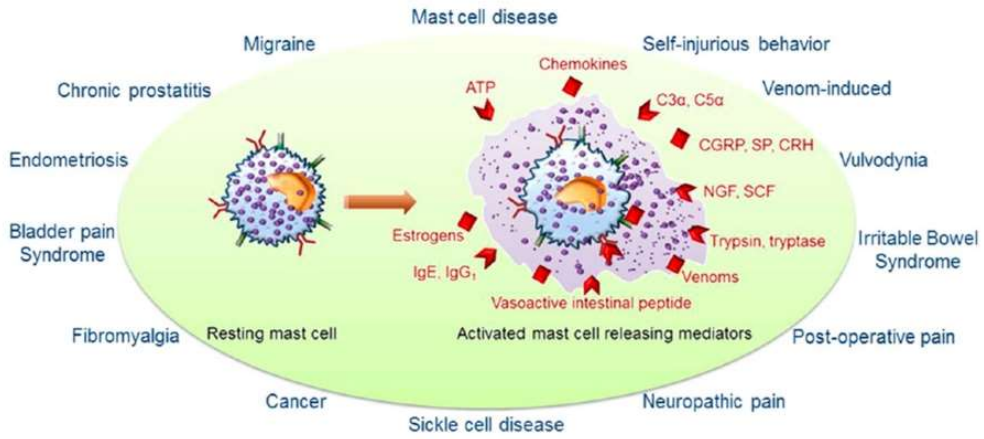


Figure 1. Mast cell-associated disease-specific pain syndromes, mast cell activation and its common activators: ATP (Adenosine tri-phosphate), chemokines, C3α, C5α (Complement 3α, 5α), estrogens, immunoglobins (IgE, IgG1), CGRP (calcitonin gene-related peptides), SP (substance P), CRH (corticotropin-releasing hormone), NGF (nerve growth factor), SCF (stem cell growth factor), trypsin, tryptase, venoms, vasoactive intestinal peptides.

Aich et al. Int J Mol Sci, 2015

Siiskonen et al. Fron. Cell. Neurosci, 2019, 13:422

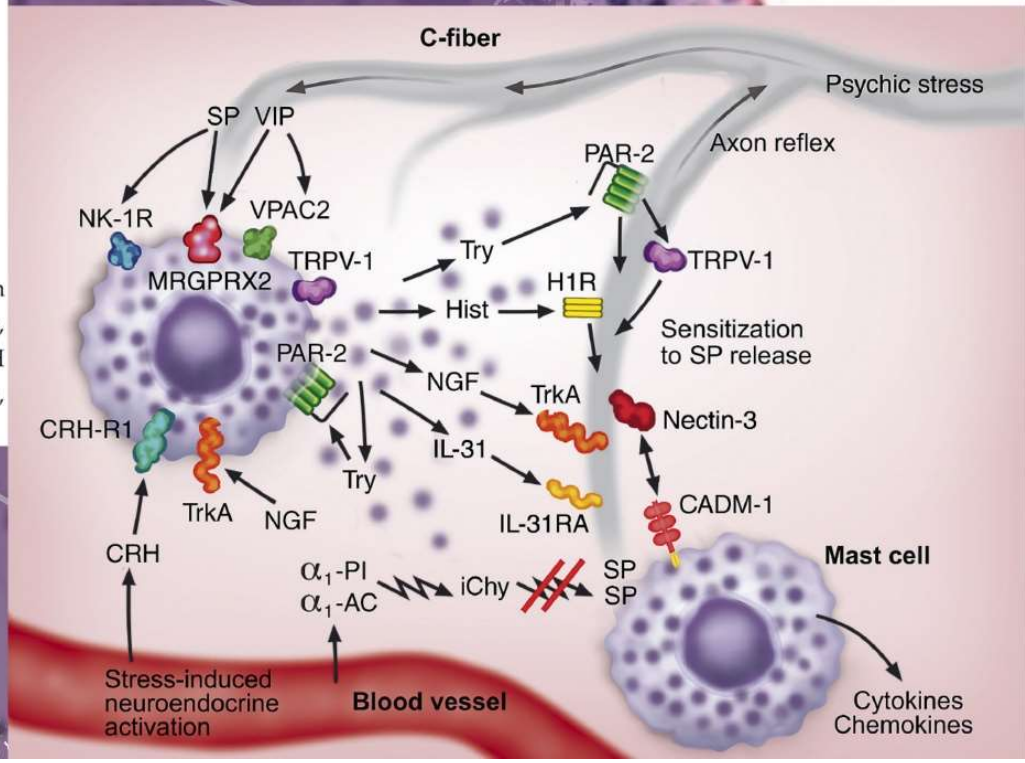


Table 1
Role of mast cells in brain inflammation.

- Activation by CRH and neurotensin
- Release of inflammatory mediators (IL-6, TNF, mtDNA)
- Release of IL-6 and TGFβ which promote IL-17 cell maturation
- Disruption of the BBB
- Recruitment of circulating lymphocytes
- Stimulation of microglia activation and proliferation
- Depletion of histamine which promotes motivation

Theoharides, 2016. Euro. J of Pharm.

key takeaways

- patients need care providers with an open mind who are willing to treat what is likely a common condition
- multisystem complaints that have a "fibromyalgia" flavour? multiple conditions requiring several meds?
  - THINK MCAS
- make your patients do the history for you. . .
- make your patients trial the easy treatments for you. . .
- while MCAS can seem overwhelming, consider approaching symptoms one at a time in order of priority to the patient
- schedule short but frequent visits

Link to view this presentation: https://prezi.com/view/Yl46H403VGDCKIP29kk8/

References

References

Afrin LB, Ackerley MB, Bluestein LS, Brewer JH, Brook JB, Buchanan AD, Cuni JR, Davey WP, Dempsey TT, Dorff SR, Dubravec MS, Guggenheim AG, Hindman KJ, Hoffman B, Kaufman DL, Kratzer SJ, Lee TM, Marantz MS, Maxwell AJ, McCann KK, McKee DL, Menk Otto L, Pace LA, Perkins DD, Radovsky L, Raleigh MS, Rapaport SA, Reinhold EJ, Renneker ML, Robinson WA, Roland AM, Rosenbloom ES, Rowe PC, Ruhoy IS, Saperstein DS, Schlosser DA, Schofield JR, Settle JE, Weinstock LB, Wengenroth M, Westaway M, Xi SC, Molderings GJ. Diagnosis of mast cell activation syndrome: a global "consensus-2". Diagnosis 2021;8(2):137-152.

Afrin LB, Butterfield JH, Raithel M, Molderings GJ. Often seen, rarely recognized: mast cell activation disease – a guide to diagnosis and therapeutic options. Annals of Medicine 2016;48(3):190-201.

Afrin LB, Molderings GJ. A concise, practical guide to diagnostic assessment for mast cell activation disease. World Journal of Hematology 2014;3(1):1-17.

Afrin LB, Self S, Menk J, Lazarchick J. Characterization of Mast Cell Activation Syndrome. The American Journal of the Medical Sciences 2017;353(3):207-215.

Aich A, Afrin L, Gupta K. Mast Cell-Mediated Mechanisms of Nociception. International Journal of Molecular Sciences 2015;16(12):29069-29092.

Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: Proposed diagnostic criteria. Journal of Allergy and Clinical Immunology 2010;126(6):1099-1104.e1094.

Alfter K, Von Kügelgen I, Haenisch B, Frieling T, Hülsdonk A, Haars U, Rolfs A, Noe G, Kolck UW, Homann J, Molderings GJ. New aspects of liver abnormalities as part of the systemic mast cell activation syndrome. Liver International 2009;29(2):181-186.

Butterfield JH. Nontryptase Urinary and Hematologic Biomarkers of Mast Cell Expansion and Mast Cell Activation: Status 2022. The Journal of Allergy and Clinical Immunology: In Practice 2022;10(8):1974-1984.

Molderings GJ, Brettner S, Homann J, Afrin LB. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. Journal of Hematology & Oncology 2011;4(1):10.

Molderings GJ, Kolck U, Scheurlen C, Brüss M, Frieling T, Raithel M, Homann J. [Systemic mast cell disease with gastrointestinal symptoms--a diagnostic questionnaire]. Dtsch Med Wochenschr 2006;131(38):2095-2100.

Molderings GJ, Zienkiewicz T, Homann J, Menzen M, Afrin LB. Risk of solid cancer in patients with mast cell activation syndrome: Results from Germany and USA. F1000Research 2017;6:1889.

Novak P, Giannetti MP, Weller E, Hamilton MJ, Castells M. Mast cell disorders are associated with decreased cerebral blood flow and small fiber neuropathy. Ann Allergy Asthma Immunol. 2022 Mar;128(3):299-306.e1. doi: 10.1016/j.anai.2021.10.006. Epub 2021 Oct 11. PMID: 34648976.

Siiskonen H, Harvima I. Mast Cells and Sensory Nerves Contribute to Neurogenic Inflammation and Pruritus in Chronic Skin Inflammation. Front Cell Neurosci. 2019 Sep 18;13:422. doi: 10.3389/fncel.2019.00422. PMID: 31619965; PMCID: PMC6759746.

Theoharides TC, Alysandratos KD, Angelidou A, Delivanis DA, Sismanopoulos N, Zhang B, Asadi S, Vasiadi M, Weng Z, Miniati A, Kalogeromitros D. Mast cells and inflammation. Biochim Biophys Acta 2012;1822(1):21-33.

Theoharides TC, Stewart JM, Panagiotidou S, Melamed I. Mast cells, brain inflammation and autism. Eur J Pharmacol. 2016 May 5;778:96-102. doi: 10.1016/j.ejphar.2015.03.086. Epub 2015 May 1. PMID: 25941080.

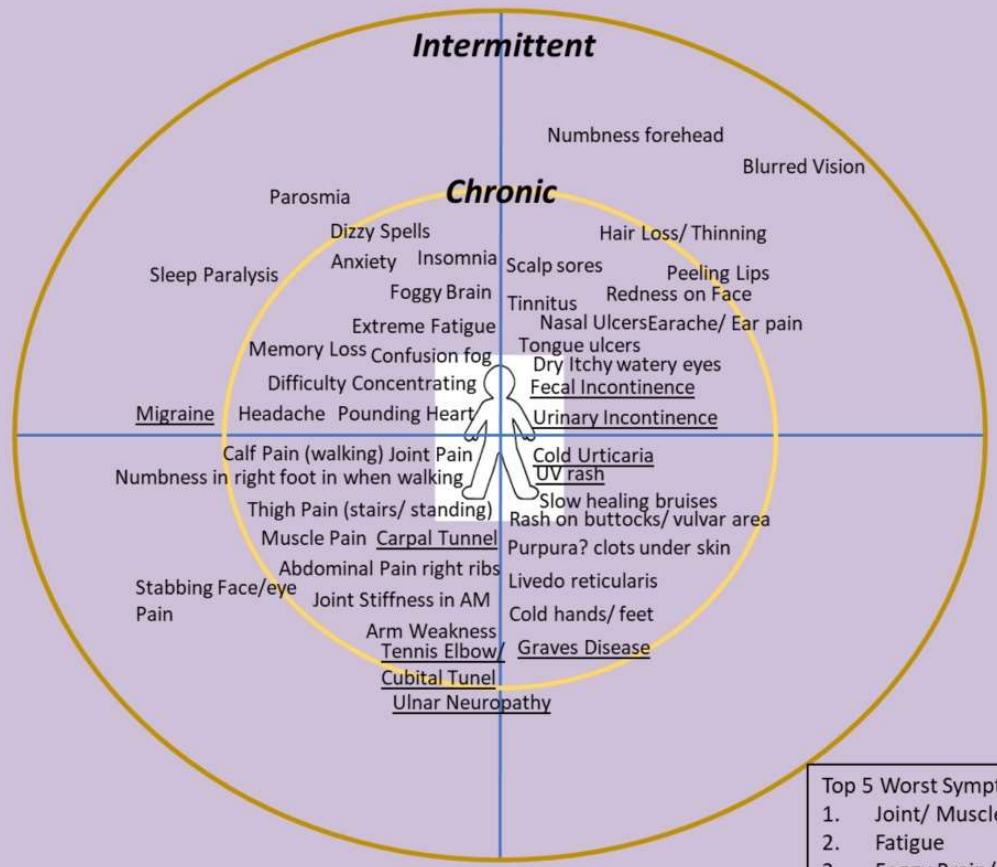
Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, Castells M, Escribano L, Hartmann K, Lieberman P, Nedoszytko B, Orfao A, Schwartz LB, Sotlar K, Sperr WR, Triggiani M, Valenta R, Horny H-P, Metcalfe DD. Definitions, Criteria and Global Classification of Mast Cell Disorders with Special Reference to Mast Cell Activation Syndromes: A Consensus Proposal. International Archives of Allergy and Immunology 2012;157(3):215-225.

Valent P, Akin C, Bonadonna P, Hartmann K, Brockow K, Niedoszytko M, Nedoszytko B, Siebenhaar F, Sperr WR, Oude Elberink JNG, Butterfield JH, Alvarez-Twose I, Sotlar K, Reiter A, Kluin-Nelemans HC, Hermine O, Gotlib J, Broesby-Olsen S, Orfao A, Horny H-P, Triggiani M, Arock M, Schwartz LB, Metcalfe DD. Proposed Diagnostic Algorithm for Patients with Suspected Mast Cell Activation Syndrome. The Journal of Allergy and Clinical Immunology: In Practice 2019;7(4):1125-1133.e1121.

Valent P, Akin C, Hartmann K, Alvarez-Twose I, Brockow K, Hermine O, Niedoszytko M, Schwaab J, Lyons JJ, Carter MC, Elberink HO, Butterfield JH, George TI, Greiner G, Ustun C, Bonadonna P, Sotlar K, Nilsson G, Jawhar M, Siebenhaar F, Broesby-Olsen S, Yavuz S, Zanotti R, Lange M, Nedoszytko B, Hoermann G, Castells M, Radia DH, Muñoz-Gonzalez JI, Sperr WR, Triggiani M, Kluin-Nelemans HC, Galli SJ, Schwartz LB, Reiter A, Orfao A, Gotlib J, Arock M, Horny HP, Metcalfe DD. Updated Diagnostic Criteria and Classification of Mast Cell Disorders: A Consensus Proposal. Hemasphere 2021;5(11):e646.

Images:
https://fineartamerica.com/featured/1-mast-cell-medimagescience-photo-library.html
https://www.researchgate.net/figure/A-common-depiction-of-the-evolution-of-the-myeloid-and-lymphoid-cell-lines-from-a_fig1_221927033
https://commons.wikimedia.org/wiki/File:2228_Immune_Hypersensitivity_new.jpg
http://www.cells-talk.com/version_act/images/download/MAST-CELLS-SAMPLE_ENTRY.pdf

Meet Lisa



Chronic – symptoms appear three days a week or more.
Intermittent – symptoms appear weekly or monthly not daily.

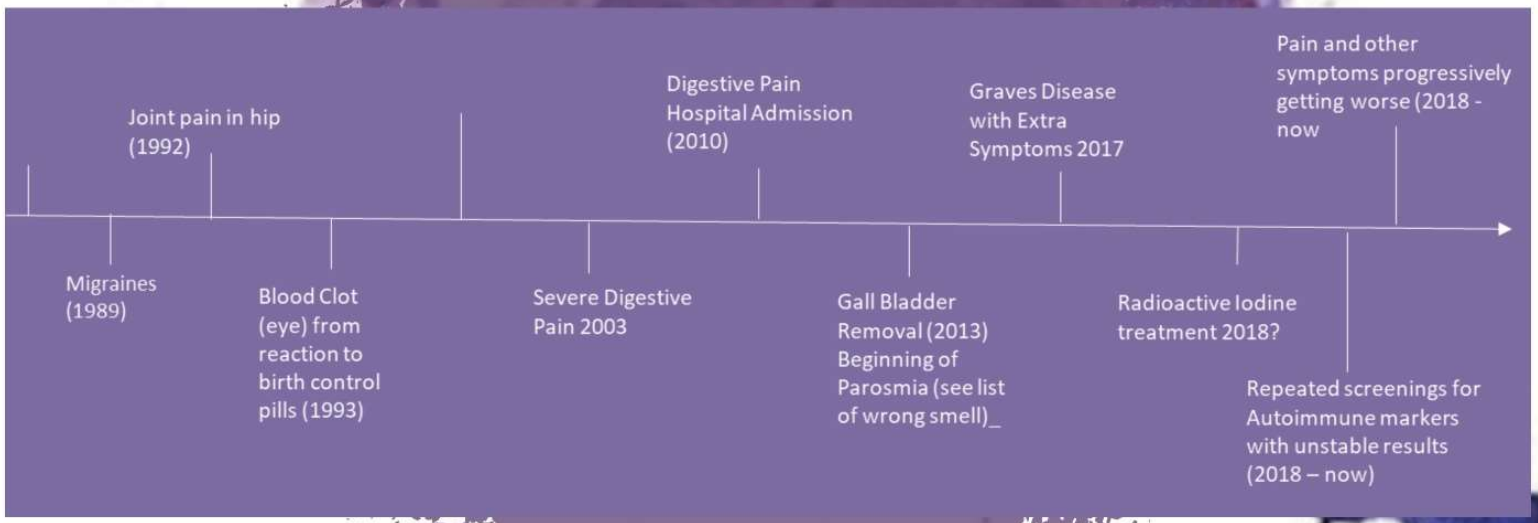
Top 5 Worst Symptoms

1. Joint/ Muscle Pain
2. Fatigue
3. Foggy Brain/Poor Concentration
4. Redness/ Rashes
5. Mouth and Nose Sores

Timeline

Initial Assessment

Follow-ups


Migraines (1989)
Joint pain in hip (1992)
Blood Clot (eye) from reaction to birth control pills (1993)
Severe Digestive Pain 2003
Digestive Pain Hospital Admission (2010)
Gall Bladder Removal (2013) Beginning of Parosmia (see list of wrong smell)_
Graves Disease with Extra Symptoms 2017
Radioactive Iodine treatment 2018?
Repeated screenings for Autoimmune markers with unstable results (2018 – now)
Pain and other symptoms progressively getting worse (2018 - now

Initial Consultation

DATE OF CONSULTATION: 18/10/2022 ; 9:00 a.m. to 10:30 a.m.

Dear Dr. [redacted]

Thank you for your referral of this 47-year-old woman to the Chronic Pain Management Program at St. Joseph's Care Group with a chief complaint of widespread arthralgia and pain. She was assessed in person and unaccompanied.

SOCIAL HISTORY
The patient is married, has 2 children, and is currently employed at [redacted] She denies financial strain. There are no legal issues pending. She has access to private insurance coverage.

ALLERGIES
No known allergies, but does report a previous reaction to unknown pain medication in the Emergency Department.

MEDICATIONS
Levothyroxine 88 mcg p.o. Monday, Wednesday, Friday, 100 mcg Tuesday, Thursday, Saturday and Sunday.

SUBSTANCE USE
The patient rarely drinks alcohol, is an ex-smoker since 2017, has a 10 year pack history, does not use any street drugs or recreational cannabis, and has no history of addiction.

PAST MEDICAL HISTORY
Recurrent Grave's disease
Hypothyroidism
Anxiety
PTSD
Carpal tunnel syndrome
Cubital tunnel syndrome
Retinal artery thrombosis due to OCP
Urinary incontinence

PAST SURGICAL HISTORY
Cholecystectomy
Bilateral breast reduction

FAMILY HISTORY
Her brother has a history of ankylosing spondylitis. Her mother has a history of coronary artery disease, and her father has a history of asthma.

HISTORY OF PRESENTING ILLNESS
The patient has been struggling with chronic right hip pain for over 30 years now in the absence of any inciting injury or trauma. She first saw a physician for this at the age of 14. She also describes the pain in the right medial thigh more recently that is stabbing, throbbing, and agonizing in nature and is really affecting her sleep in recent months. She reports multi-site joint pains. She describes intermittent hypoesthesia and weakness to her right lower leg in a stocking pattern and also endorses occasional random paresthesias in other areas of her body. Finally, she endorses headache symptoms.

The worst pain is localized to her right greater trochanteric area. It is constant and activity dependent. She describes the pain as a pressure in nature and on average rates her pain as 8/10, 6/10 at best and 9/10 at worst. Aggravating factors include walking. She has not found any alleviating factors for this. She has associated symptoms of snapping and popping sensations to her hip, stating she has felt this throughout her lifetime, and also has noted being able to "pop her hips out" on demand. Previous therapies tried have included exercise and at one point was told to take ballet to deal with this hip issue, and also stretching exercises. She has not had formal physiotherapy for this problem.
Her headaches occur 15 plus days per month, and of these, 11 to 12 are migrainous. The headaches usually last all day. They are bilateral, localized to the occiput, then radiating anteriorly to her eyes and temporal region. They are throbbing and pulsatile in nature, moderate to severe in intensity, and aggravated by activity. These headaches are associated with nausea, photo and phono sensitivity. There are associated symptoms of aura with "sparkly lights" that precede the headaches. There are autonomic symptoms of tearing and rhinorrhea during headaches. There are no red flag symptoms.

A review of systems reveals that her weight is stable, her appetite is adequate but energy levels are very low. A skin review reveals that she rashes rather frequently, which is easily triggered by sun or cold and presents with and without hives. They predominantly occur to her upper chest and face. She endorses burning and pruritus to her eyes. A cardiac system review reveals she has ongoing symptoms of tachycardia and palpitations and often feels symptoms of orthostatic hypotension upon rising too quickly. As such, he has learned to rise very slowly as she has found if she does not, she feels somewhat presyncopal. Her sleep is of poor quality and she has difficulties falling asleep and staying asleep due to pain. She feels tired upon wakening and in recent months with the right medial thigh pain has only been sleeping 3 hours per night. She does not use any sleeping aids. A bowel screen reveals that she has longstanding symptoms of loose stools and now also reports anal leakage on a daily basis for which she is being referred to Toronto for possible surgical correction. A bladder screen reveals symptoms of stress incontinence and she has also briefly been seen by pelvic floor physiotherapy, but she could not maintain ongoing sessions to try and treat this. A musculoskeletal screen reveals symptoms of hypermobility to her hips, ankles, and fingers. Her Beighton score was 3/9 to the left knee, left thumb and she was able to place her palms on the floor. A mental health screen reveals that she has felt substantially more anxious in the last 3 years and she feels this is as a result of 2 traumatic events that have occurred during this time period. A PHQ-9 score was 15, or moderate for symptoms of depression, and a GAD-7 score was 18, or severe for symptoms of anxiety.

Mast Cell Mediator Release Symptoms (validated questionnaire for mast cell activation syndrome): scored clinically positive with a score of 23, where a score greater than 14 supports a clinical differential of MCAS.

Given her joint symptoms, an Ehlers-Danlos Syndrome Checklist was completed to review for possibility of meeting diagnostic criteria, for which she does not at the present time meet criteria, but seems to be on the hypermobility spectrum.

PREVIOUS INVESTIGATIONS
She has had an extensive work up completed by Dr. [redacted] looking at various autoimmune contributors. She has on 2 occasions had a positive ANA screen, but then subsequent follow up screens were negative. She also at one point had a positive CRP. None of the investigations were overwhelmingly supportive of an autoimmune arthritis as a contributor. Previous B12 screening was in the low normal range.

PHYSICAL EXAMINATION
The patient appears her stated age and is alert, pleasant and cooperative throughout the exam. Her mood appears euthymic.

Musculoskeletal exam revealed a normal gait, posture with normal anatomical curvature of the spine. Hip joint exam was normal with no pain on joint loading or with figure-eight motion. Sacroiliac joint testing was negative with the exception of a positive FABER's test on the right. There was pain with palpation to her medial thigh with associated signs of allodynia and hyperalgesia on pinprick testing and light brush. There was no pain over the greater trochanter on either side and localizing her pain in this area was actually most notable to the origin of the quadriceps muscles, particularly noting a taut vastus lateralis. Following around, the patient also had significant pain to the gluteus minimus, gluteus medius, and piriformis muscles on both sides, but right substantially worse.

I did review her skin and she does have telangiectasias present, dermatographism was present, and review of pictures of previous rashes do show typical urticarial rashes, some also notably with hives, and predominantly occurring to the upper chest, or exposed arm and leg surfaces when exposing herself to the sun, even for short periods reportedly.

PATIENT EXPECTATIONS/GOALS OF TREATMENT
The patient is hoping for diagnostic clarification and is open to any suggestions that may be helpful for managing her symptoms.

WORKING DIAGNOSIS
Deep Gluteal Pain Syndrome, right worse than left.
On the hypermobility spectrum.
Query Mast Cell Activation Syndrome.

PLAN
Education was provided to the patient regarding the nature of her pain. While she does not meet criteria for hypermobile Ehlers-Danlos Syndrome, given the snapping nature of her hips that seems to be worse with walking, I have found that with hypermobile or Ehlers-Danlos Syndrome patients that a sacroiliac joint belt, while not specifically intended for the hip joints, has often been helpful in controlling this pain while active with walking. Given her hypermobility, I do not feel that stretching is likely to be a useful approach for her symptoms. She will likely need to manually release some of the spastic muscle areas with a trigger point wand and hopefully we will be able to counsel her with some isometric relaxation exercises to reduce the overall tone to the affected muscle groups.

With respect to the patient's question as to whether or not she has fibromyalgia, certainly on the face of it, she meets criteria, however I do find that fibromyalgia is likely to be a heterogenous group of disorders of which a lot of her symptoms may be better explained by Mast Cell Activation Syndrome. While the patient does not have any specific allergies or known anaphylaxis, this is not required to meet criteria for this syndrome. Unlike systemic mastocytosis, this is at non life-threatening syndrome, albeit symptoms are similar and overlapping. I counseled the patient that this is a relatively new medical entity in the literature and as of yet, there is not consensus in the medical community as to the best approach to diagnose and treat it. I include a good overview article for interested clinician review of the syndrome: https://pubmed.ncbi.nlm.nih.gov/32324159/. While she meets clinical symptom criteria, this does not mean that she satisfies the overall criteria as of yet. It is recommended to have 2 positive lab markers of which the only 2 we have available in our area is tryptase and chromogranin A. Tryptase is unlikely to be positive in the absence of a history of idiopathic anaphylaxis and does require a second test while the patient is highly symptomatic, which is very difficult to logistically obtain. Chromogranin A is a non-specific marker, however in the context of not meeting criteria for other causes of elevated chromogranin A, can be supportive. Our best bet is to request that the previous biopsies of her duodenum that showed signs of inflammation have a mast-cell CD117 stain applied to assess for counts per high-powered field of greater than 19. This would satisfy objective criteria and I will request this from pathology.

Finally, the third criteria is response to any antihistamines or mast cell stabilizers. As such, the patient was given a list of over-the-counter antihistamines to try for up to 2 weeks at a time, and note any benefits with each. It typically does not take long to determine if any one of these is likely to be helpful for long-term control of symptoms and can certainly be helpful for widespread pain, pruritus, but even symptoms such as brain fog or joint pain. As many patients do not achieve significant enough symptom control with over-the-counter antihistamines alone, we can consider at follow up mast cell stabilizers such as Ketotifen or Cromolyn, which I have had some degree of success in other mast-cell patients in achieving pain control.

Referrals will be made in program to see our occupational therapist for brace support of her ankles and knees to protect her joints long-term. Physiotherapy will be asked to see to support the patient with isometric relaxation exercises.

We did not address all of the possible concerns today and at follow up we will need to look in more depth at her headache history to see if there are other options that we can use to reduce the frequency of her migraines.

Follow up will be arranged in 3 months' time.

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