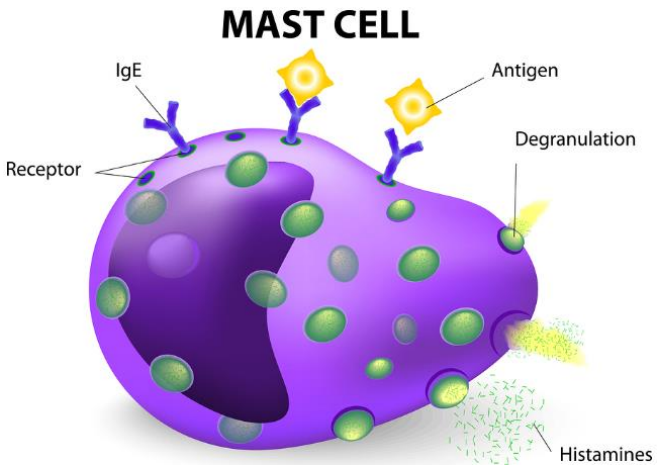
Do I Have Mast Cell Activation Syndrome (MCAS)?

Mast Cell Activation Syndrome (MCAS) is a disorder where components of the blood stream, namely mast cells, secrete various substances which can be involved in an allergic reaction or inflammatory reactions. However, before discussing MCAS, we need to understand what the mast cell is and where it comes from.



Mast cells come from more undifferentiated-type cells in the bone marrow. They usually mature in various tissues. Mast cells are important reactionary cells in allergic reactions and in inflammatory reactions. They secrete substances, such as Histamine, Prostaglandins, Leukotrienes, various enzymes which can break up other substances known as Proteolytic enzymes and Cytokines, such Interleukins 6, 18 and 13. Also, Tumor Necrosis Factor (TNF) and Vascular Endothelial Growth Factor (VEGF) may be secreted. These substances may cause inflammation and also activate the immune system in various circumstances. Normally, mast cells do not spontaneously secrete these substances but in disorders such as MCAS they can. Common triggers for mast cells to secrete these substances include IgE and antigens during an allergic reaction, anaphylatoxins, Cytokines, hormones, and substances such as Substance P (SP). In fact, SP may be the main trigger in many skin disorders such Contact Dermatitis, a disorder in which mast cells are activated and secrete many of the substances named above. In addition to Contact Dermatitis, Mast cells are very importantly involved in many other skin abnormalities, immunological responses, gastrointestinal responses, and may, interact and affect virtually every organ in the body.

MCAS is a chronic condition involving multiple organs in which normal mast cell activation leads to the inflammation and allergic symptoms that may occur episodically in patients. Gastrointestinal symptoms are common including Irritable Bowel Syndrome. Recently, the term mast cell activation syndrome disease (MCAD) has been defined. This is the major heading for MCAD with two main categories. One is known as Systemic Mastocytosis (SM) and MCAS. Both of these disorders may have similar symptoms and systemic manifestations. Usually with SM and its subclass, Mast Cell Leukemia (which is very rare), there is a genetic or clonal abnormality and there is usually an abundance of mast cells produced or a higher quantity exists; whereas, in MCAS, the number of mast cells are not increased, they are only hyperactive. It is not known if MCAS can be transferred over time into the rare neoplastic or malignant states of SM and Mast Cell Leukemia.

The triggers of MCAD include stress, food, alcohol, and various medications including possibly aspirin, infections, air pollution, heat, mold, chemicals, and changes in our intestinal microbiome. The latter may be affected by antibiotics or stress.

What is the definition of MCAD? Over the last ten years, much has been devoted towards establishing a clear definition for this disorder. Criteria have been proposed, and three criteria are specifically agreed upon. It is important to satisfy all three criteria before concluding that the given patients' symptoms are due to mast cell activation. It should be recognized that idiopathic anaphylaxis is a specific entity within the MCAS. A patient may, however, experience urticaria or hives or gastrointestinal symptoms after exposure to a possible trigger allergen.

While many of the symptoms of MCAS (see below) are nonspecific in nature, again, there are specific criteria that must be fulfilled before one can diagnosis a patient as having MCAS. There have been many criteria, but the ones most commonly used require symptoms consistent with chronic recurrent mast cell release. These include:

1. Recurrent abdominal pain, diarrhea, flushing, itching, nasal congestion, coughing, chest tightness, wheezing, lightheadedness, or a combination of some of these.
2. Laboratory evidence of a mast cell mediator (elevated Serum Tryptase) whether at baseline or with provocation or during an attack, N-methylhistamine, Prostaglandin D2, or 11-Beta-prostaglandin F2 alpha, Leukotriene E4 and other mediators as determined by various laboratory measurement that pertain to mast cells.
3. Improvement in symptoms with the use of medications that block or-treat elevations in these mediators, specifically Histamine blockers and other mast cell stabilizers.

Symptoms of MCAS can derive from any organ system and one usually needs two organ systems or comorbidities of at least two organ systems to fulfill criteria #1 above.

In regard to constitutional symptoms, fatigue and weakness, heat and cold sensitivities and sleep deprivation are commonly identified.

Dry eyes, red itchy and red burning, runny nose, and inflammation ulcers of the mouth may be seen in the head and neck organ system.

In regard to the chest and heart, chest discomfort, rapid heartbeats, redness, flushing of the skin, sudden dizziness, hot flashes, and blood pressure surges may be seen. Also, syncope and presyncope.

In regard to the pulmonary system, dry cough that occurs repeatedly, shortness of breath, difficulty taking a deep breath, and episodic asthma and wheezing-like complaints can be present.

For the gastrointestinal system, abdominal symptoms are common to include pain, crampy or spastic discomfort oftentimes associated with diarrhea, abdominal bloating and distention, and symptoms of irritable bowel syndrome and diarrhea is also noted. Swallowing difficulties and throat tightness are also noted.

In regard to the urinary tract and pelvis, bladder and pelvic pain as applies to both men and women may be present. There may be painful, frequent and urgent urination or pain during sex. The disorder of Interstitial Cystitis has been described where it is believed mast cells are very operative in its presentation and where an individual has significant urinary tract symptoms and discomfort, but does not have a documented urinary tract infection.

Neurological symptoms may occur with headaches, brain fog and neuropathic leg or arm pain.

The skin is one of the most affected organ systems by mast cells. Hives, itching, swelling of the lips, cheeks, eyelids, reddish-brown spots under the skin and occasional hemangiomas are noted. One may see reddish or pale complexion, itchiness with a burning feeling, and Dermatographism is common.

In regard to the hematologic system, one can see bruising and unusual nose bleeds.

In regard to the bones, patients can demonstrate bone pain.

Also, immune system involvement can be noted. There have been immunological disorders, such as Common Variable Immunodeficiency Syndromes associated with MCAS. One needs to determine if they get head colds or upper respiratory infections frequently and if they turn into bacterial infections, such as bronchitis and sinus infection which are common, and do these infections come on with attacks episodically that are related to mast cell activation.

Various physicians will order different tests to determine if there is an increase in mast cell mediators. Oftentimes all of these tests can come back negative for MCAS, but during attacks if these mediators, specifically Serum Tryptase, are tested during the first 1-4 hours, we can see a rise above baseline and can confirm objective data to support their diagnosis. As mentioned, Serum Tryptase is an important mediator, and during an attack one likes to see at least a two-fold plus 20% increase in this value to consider that significant. At times, Tryptase will be elevated at rest, and if it is above six (6.0), one may have to look towards a genetic enzyme abnormality. Histamine can be measured in the plasma and its metabolite N-methylhistamine can be measured in the urine, and plasma histamine in the blood. We often like to see this number more than 10 times the upper limit of normal, but any elevation is important. Prostaglandin D2 in the plasma is also measured as Heparin or Factor 8. Chromogranin A, which is nonspecific and can be seen in neuroendocrine tumors and other gastrointestinal disorders or can be elevated in renal failure. If increased, it is very suspicious for MCAS in patients who do not have the former disorders. The Leukotriene E4 in urine is also an important mediator to test for. Another important mediator to test for in the urine is PG-D2 or 11β PG F2α. In addition, many times a biopsy is taken of the skin or the GI tract during endoscopy or colonoscopy. If focal or disseminated infiltrates or morphologically inconspicuous mast cells are seen, or a mast cell collection, or a morphology of spindle shaped mast cells or if they are specially stained for CD25-positive mast cells, this gives significant strength to the diagnosis of MCAS.

One has to exclude other disorders which may mimic MCAS to make sure the symptoms are not due to Diabetes, Porphyria, Thyroid diseases, Amyloidosis, Hepatitis, Gallbladder disease,

infectious Enteritis, Carcinoid tumors, Pheochromocytoma, (a tumor of the adrenal gland which can elevate blood pressure), pancreatic endocrine tumors, Eosinophilic Syndrome abnormalities, hereditary Angioedema, Vasculitis and rarely, intestinal Lymphomas.

Treatment of MCAS or suspected MCAS is important because a response fulfils one of the criteria above. Usually we begin with H1-antihistamines, such as Cetirizine (Zyrtec*), Ketotifen (Zaditor), or Fexofenadine (Allegra) or Loratadine (Claritin). H2-histamines, such as Famotidine (Pepcid*) or Ranitidine (Zantac) are added on. This is usually first-line treatment using both an H1 and an H2 agent. If the response is not complete, we often go to Antileukotrienes, such as Montelukast (Singulair) or Zileuton (Zyflo). Some people use natural products, such as Curcumin or St. John's wart. If not contraindicated, or not determined to be a triggering agent, a nonsteroidal anti-inflammatory (NSAID) agent and aspirin can be helpful in reducing inflammation in some of the patients. Oftentimes, we will tailor the therapy if a certain mediator is tested for and is elevated in the urine or blood. For example, Prostaglandin elevation may influence us to use nonsteroidals or aspirin earlier. Disodium Cromoglycate (Cromolyn), is a mast cell stabilizer that is used in cases of MCAS that have not responded to the above treatment with antihistamines and Leukotriene inhibitors. It can be given as a liquid four times day or even inhaled. Biological agents are usually used only in severe cases that are refractory to treatment and beyond the scope of this review.

One should note that there is also a natural substance which has been found to occasionally be effective as a mast cell stabilizer and may be more effective than Disodium Cromoglycate (Cromolyn). This is Quercetin, which is a Flavonoid. On cultured human mast cells, Quercetin has been shown to inhibit the secretion of Histamine in PGD2. In addition to inhibiting Histamine, Leukotrienes and PGD2 from primary human cord blood-derived cultured mast cells stimulated by IgE/anti-IgE. In fact, it has been shown in tissue cultures to be more important than Cromolyn as a mast cell stabilizer.

If too many mediators are spilled into one system they may experience anaphylaxis, which includes difficulty breathing, itchy hives, flushing, pale skin, a warm feeling, weakness, and rapid pulse, low blood pressure, nausea, vomiting, diarrhea, and dizziness. With low blood pressure one can have syncope or fainting. There has been a relation between hypermobile Ehlers-Danlos syndrome (hEDS), Postural Orthostatic Tachycardia Syndrome (POTS) and MCAS. To date, it has not been proven unequivocally that there is a cause and effect relationship between these entities. Many believe that the pathophysiology of POTS can involve a mast cell activation etiology which can overlap with other types of etiology, such as hyperadrenergic, hypovolemic, neuropathic, and so forth. The problem is that there are vague overlapping symptoms that one sees with POTS and hEDS. Many autonomic dysfunction symptoms (Dysautonomias) can be seen with people with MCAS, such as lightheadedness, dizziness, fainting, rapid heartbeat, blood pressure changes and so forth, and there may not be as close an association as is often thought.

Many patients present with symptoms that are suggestive of MCAS and significant skin abnormalities, such episodic rashes, hives, and generalized itching. If two organ systems are involved with symptoms, one should begin to think that they may have an MCAS problem. Appropriate laboratory testing should be done. As the laboratory testing takes some time to be sent back to the physician's office, empiric treatment should be started with antihistamines and H1 and H2 blockers. Many patients will have a significant response. This is very suggestive. However, a third criteria really needs to be fulfilled for a precise diagnosis, and if the urine and blood testing comes back negative, one could presume that the patient has MCAS, but it still does not meet all three criteria. We will often have a patient repeat the blood test during an acute episode to see if the Tryptase, Histamine or any of the blood components rise significantly. There has been some suggestion that the Mayo Clinic has developed a spot-urine test to also be taken.

We see many of our patients tested in the autonomic laboratory that have both EDS and MCAS. We believe this is a strong interrelationship and not just an association of commonly found problems that occur frequently in people. While MCAS is becoming more frequently recognized now that we have diagnostic criteria, it is still not that common of a disorder to be aggregated with Ehlers-Danlos syndrome (which can be found in up to 5% of people) or autonomic dysfunction (orthostatic intolerance is becoming more commonly recognized in our population).