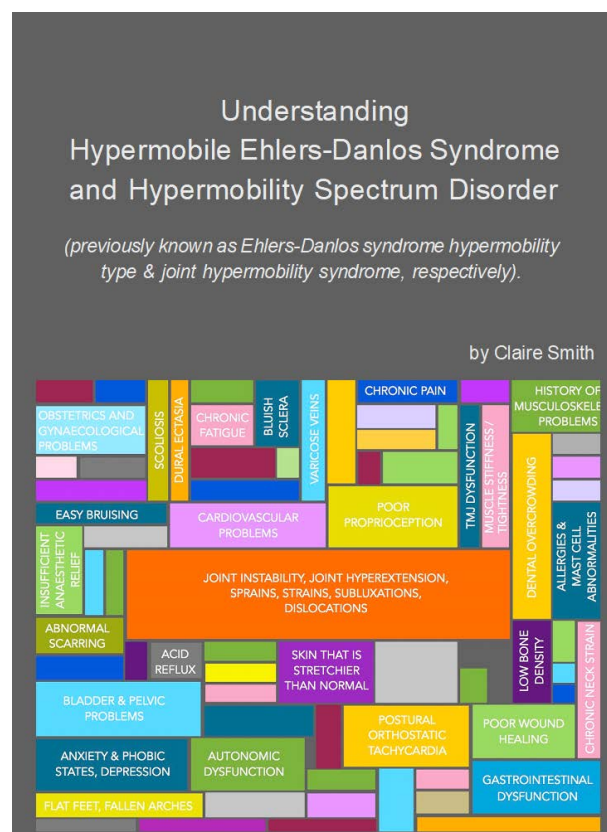


Mast cell activation syndrome and hEDS/HSD

The following extract is taken from:
Understanding hypermobile Ehlers-Danlos
Syndrome and Hypermobility Spectrum
Disorder

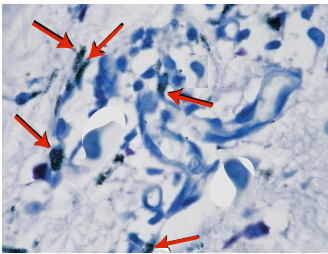
Chapter 2

Part 1 - Widespread symptoms & comorbidities



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Mast cell activation syndrome

Introduction

Mast cell activation and a possible relationship with hEDS/HSD is a frequent topic of discussion on hypermobility-related forums and social media, and its wide-reaching manifestations are a debilitating phenomenon for many, with symptoms that include skin rashes, flushing, itching, nausea, headache, abdominal cramping, diarrhea, vomiting, respiratory symptoms, hypotension, tachycardia, unexplained arrhythmias, and neurological manifestations (Akin C. et al 2010). When it comes to identifying hard scientific evidence of a link between the two, however, it becomes apparent that research is still in its very early stages. In this section, we will look at mast cell activation and consider some hypotheses put forward by leading experts.

What are mast cells?

Mast cells are part of our immune system and are vital to our health. They play a protective role, defending our bodies against allergens and pathogens such as bacteria, viruses and parasites, that can cause disease or illness (Prussin C. & Metcalfe D. 2003). They also assist in wound healing (Jung M. 2013), accumulating in high quantities close by the site of injury and surrounding nerves.

Mast cells reside within connective and mucosal tissues located in the skin, respiratory system (mouth, nose and lungs), linings of the stomach, intestine and urinary tract, as well as near blood and lymphatic vessels, within nerves, and in the brain (Encyclopedia Britannica). They can tell the difference between different sorts of stimuli and, where necessary, respond accordingly by releasing pro-inflammatory mast cell mediators (frequently referred to as a kind of chemical 'alarm system'), including histamine, proteases, prostaglandins, leukotrienes and cytokines - a process known as degranulation.

The resulting inflammation is the body's protective response against allergy and infection. The 'chemical

alarms' draw other components of the immune defence team such as immune cells, clotting proteins and signalling molecules, to areas of the body where they are needed (2/NIH). Histamine induces fluid secretion at the site of infection, in order to rid the body of infectious agents or allergens, and it causes the muscle walls surrounding blood vessels to relax allowing white blood cells to move easily to the site of infection (Pollock J. 2006). This process also causes less desirable manifestations that we commonly associate with allergic reactions, ranging from itching, sneezing and a runny nose, to flushing, swelling, hives, nausea, bloating, abdominal pain, and, in extreme cases, anaphylaxis (British Society for Immunology).

Systemic mastocytosis and mast cell activation syndrome

According to Dr. Andrew White, specialist in allergy and immunology, physicians usually think of mast cell mediator release as an '*all or nothing*' phenomenon, in which mast cells are either resting quietly doing nothing, or are busy releasing high quantities of mediators in response to an allergic reaction. In his opinion, however, this is probably not the case. He explains: '*...mast cells are constantly interacting with the environment – sensing – reacting. And in some people, this process might not work correctly.*' Indeed, for reasons not yet fully understood, mast cells in some people can go into a state of excessive activity, reacting to things that they should ignore and releasing large amounts of chemicals (pro-inflammatory mediators) such as histamine, into the system, both spontaneously and in response to trigger stimuli (Mouderings G.J. 2011).

This excessive mast cell activity and mediator release is seen in a group of conditions known as mast cell activation disorders (see **Box 2**), of which mast cell activation syndrome is one. In order to understand mast cell activation syndrome (MCAS), we must first look a little more closely at a rarer, but perhaps, better known disorder called systemic mastocytosis (SM).

The clinical manifestations, shown in **Box 1**, have long been defined in literature as being associated with SM, a disorder in which symptoms are caused by an abnormal accumulation of malformed and functionally abnormal mast cells that gather in one or more organ system (Valent P. et al 2007). Recently, however, experts have identified another category of patients who share many similarities with those who have SM. They

Box 1.**Clinical manifestations of SM (and MCAS) include:**

- Easy flushing from the chest upwards (triggered by certain foods, heat, stress etc).
- Dermatographia (ability to *write* on the skin with a light scratch that turns red in a minute).
- Chronic fatigue.
- Eyes that feel gritty, sore, watery, or have difficulty focusing.
- Hypotension (low blood pressure).
- Infections (bronchitis, rhinitis, and conjunctivitis).
- Anaphylaxis.
- Angioedema (swelling around lips or eyes).
- Bone pain, bone loss, osteoporosis, osteopenia, osteosclerosis.
- GI pain, bloating, cramping, gas, abdominal pain, gastroesophageal reflux.
- Malabsorption.
- Reactions to some local and general anesthetics (may include abdominal pain, diarrhea, vomiting, hives).
- Food and drug allergies or sensitivities (may be negative on IgE test but you still react, often increasing).
- Sensitivity or allergy to alcohol, especially red wine.
- Hives.
- Urticaria pigmentosa (reddish brown spots, ranging from the size of freckles to larger patches).
- Rashes (with or without itching).
- Muscle pain.
- Itching.
- Brain fog.
- Headaches.
- Oesophageal spasms.
- Wheezing, coughing, sudden congestion or sneezing, difficulty breathing.
- Nighttime waking.
- Sensory processing disorders.
- Anxiety and panic attacks - in order to counter-act the over production of histamine, the body may also react by producing adrenaline which helps to de-activate histamine. This can sometimes cause anxiety and panic attacks.

Symptoms of MCAS vary greatly from person to person. Some experience only one or two symptoms whilst others experience symptoms which are severely debilitating (Castells M. 2006)

Symptoms sources: Lee J.K 2008 / oreds.org / Castells M. 2006 / Pollock J. 2006 / Seneviratne S.L. et al 2017)

present with the same classic signs and symptoms of episodic mast cell activation, but fail to meet the World Health Organisation's criteria for mastocytosis, because investigators have been unable to find any mast cell abnormality or external triggers that could explain these episodes (Alvarez-Twose, I. 2010 / Hamilton, M.J. 2011 / Alvarez-Twose, I. et al 2012 / Picard M. et al 2013).

It is instead hypothesized that, in *these* patients, their otherwise normal mast cells are hyper-responsive to everyday stimuli (Akin C. et al 2010). The term 'mast cell activation syndrome' has been introduced in order to provide a diagnosis for such individuals (Mouldering G.J. 2011).

Both SM and MCAS are capable of affecting functions in all systems, organs and tissues of the body; particularly the skin, gastrointestinal tract and the cardiovascular and nervous systems (Akin C. et al 2010 / Frieri M. 2013 / Patient.co.uk).

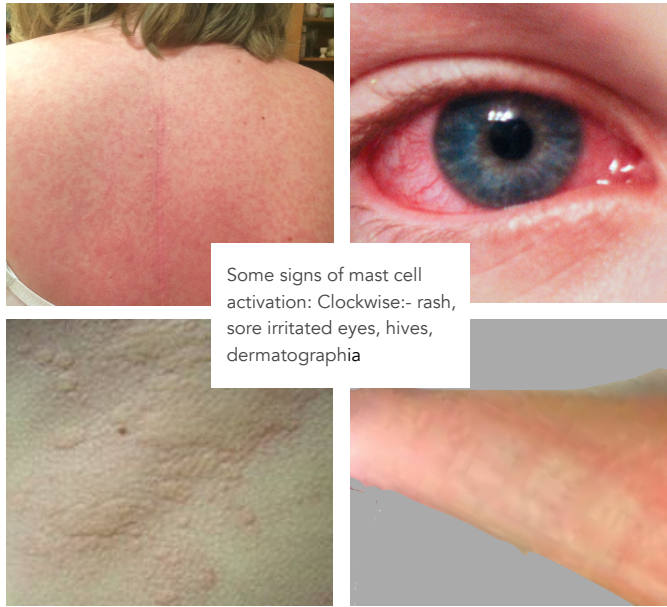
Episodes of MCAS and SM can happen at any time, severely affecting a person's quality of life. Patients describe a 'minefield' of triggers and symptoms which significantly disrupt their lives. Valerie Slee, Vice Chair of the Mastocytosis Society agrees, saying: "*Living with Mastocytosis or MCAS can be very difficult, primarily because of the unpredictability of the symptoms. You can feel perfectly fine when you wake up in the morning, dress to go somewhere, then, just as you are going out the door you get chest pain or abdominal pain and your plans are waylaid.*"

Box 2.**Examples of mast cell activation disorders**

- Idiopathic MCADs (there is no identifiable cause): Examples include **mast cell activation syndrome** and anaphylaxis.
- Primary MCADs (the result of a single primary cause): Examples include systemic mastocytosis, cutaneous mastocytosis, mast cell sarcoma, monoclonal-mast-cell syndrome and mast cell leukemia.
- Secondary MCADs (caused by another condition): Examples include drug reactions, allergies and some types of chronic infection or autoimmune dysfunction.

The disorders within this group differ in their severity and can involve various organ systems

(Akin C. 2014).



Potential triggers:

Some of the many 'normal' stimuli that can trigger episodes of MCAS include:

- Foods and drinks that are high in histamine or are known to trigger histamine release.
- Injuries such as cuts and bone fractures.
- Some pain medications such as aspirin, NSAIDs and narcotics.
- Strong scents including perfumes and chemicals.
- Friction, pressure, or vibration on the skin.
- Extremes of temperature.
- Exposure to sunlight.
- Exercise.
- Emotional and physical stress / excitement.

(Mastocytosis [& MCAS] Society Canada / Patient.co.uk)

MCAS and a possible association with EDS/HSD

There seems to be a growing awareness in the medical and patient community that some patients with EDS/HSD also have signs and symptoms of mast cell activation (MCA). Indeed, results of a recent case control study by Dr Ingrid Cheung *et al* showed that two thirds of the patients, with a formal diagnosis of POTs and EDS, also had validated symptoms of a mast cell disorder suggestive of MCAS, based on diagnostic criteria and validated symptoms as reported by Akin *et al* (2010).

Writing in a recent publication (Fragile Links, spring 2015), Dr Brad Tinkle, clinical geneticist and expert in EDS, states that at the moment, he can't explain the connection between EDS and MCA, but the more he asks, the more (EDS) patients he finds who describe signs and symptoms of histamine excess (5/EDS Support UK).

It would seem this is a complicated intersection of two poorly understood illnesses for which further

investigation is crucial, not only to validate patients symptoms, but also to improve the treatment approach for those affected.

In the meantime, we will consider a few areas of research which could provide some clues as to why people with EDS/HSD may also experience symptoms of mast cell activation:

The first clue relates to the high prevalence of food allergies found in those with EDS. In 2010, Dr Clair Francomano, a geneticist with a special interest in disorders of connective tissue, formed part of a team whose findings confirmed a high prevalence of food allergies in those with EDS when compared to the general population, and showed a significantly higher incidence of gastrointestinal signs and symptoms such as constipation, irritable bowel syndrome, gastroesophageal reflux disease, and chronic abdominal pain. The team's observations led them to postulate that a correlation exists between food allergies and gastrointestinal dysfunction in some EDS patients, which they believe could be caused by collagen abnormalities. The team think that collagen abnormalities may allow lesions to form in the tissue of the mucosal membrane barrier. In 'normal' patients, this barrier prevents most large molecules passing from inside the bowel into the bloodstream, but the team hypothesize that altered tissue integrity in those with EDS/HSD increases the chance of larger proteins (such as undigested food particles or antigens found on the surface of cells), crossing the mucosal barrier and triggering an immunogenic response that would include mast cell activation (Zhang H. & Francomano C.A. 2010).

Further clues to mechanisms that may link EDS with mast cell activation can be found in a common comorbidity of both disorders; a subset of autonomic dysfunction called postural orthostatic tachycardia syndrome (POTs).

POTs is a disorder characterised by orthostatic intolerance and manifestations such as tachycardia, nausea, intolerances to heat and cold, flushing, brain fog, lightheadedness, fainting, breathlessness, fatigue, IBS-like symptoms and more which are, in fact, not dissimilar to symptoms seen in MCA.

In 2005, Shibao *et al* evaluated patients diagnosed with chronic disabling orthostatic tachycardia associated with episodes of systemic MCA. The number of patients involved was small, so the team

prostaglandins and leukotrienes are usually measured in a 24 hour urine sample. If the symptoms fit, the patient has evidence of making too much mast cell mediator, and treatment with medications that block or treat the substances are effective, then many physicians are then willing to diagnose MCAS.

New proposed criteria for the diagnosis of MCAS was put forward by Dr Chem Akin et al in 2010 and, although MCAS is not yet internationally recognised, it is hoped this will be formally adopted over the coming years, resulting in better understanding and treatment for patients.

In the meantime, Dr Lawrence Afrin, a hematologist specialising in mast cell disorders, and Dr Suranjith Seneviratne, Consultant in Clinical Immunology and Allergy at the Royal Free Hospital and University College London, and Director of the Centre for Mast Cell Disorder, recommend doctors look for:

- symptoms indicating chronic/recurrent abnormal mast cell mediator release,
- and, at least partial response to therapy targeted against mast cells or their mediators,
- laboratory evidence of such release (or of mast cell proliferation not meeting World Health Organisation criteria for systemic mastocytosis),
- absence of any other evident disease which could better explain the full range of findings in the patient.

Treatment

Prof. Seneviratne and his team in London are at the cutting edge of research and treatment of mast cell disorders, seeing what he believes to be the highest number of MCAS patients in any country in the world (close to 1000 as of Sept 2016). He hopes that their work will enable many more questions to be answered over the next few years.

In the meantime, however, there is no cure for MCAS, so treatment is primarily aimed at controlling and relieving symptoms. All or some of the same mediator-blocking medications used to treat SM may be used e.g. mast cell stabilisers and H1 and H2 antihistamines (Gerhard J. 2011). If patients are able to identify potential triggers for their symptoms (e.g. dietary, chemicals, medications, allergens), desensitisation therapy can be considered. Patients may be advised to follow a low histamine diet in general and, where required/possible, to make environmental modifications in order to reduce exposure to known triggers. Proton pump inhibitors may also be prescribed; if needed for stomach hyperacidity and, where tolerated, nonsteroidal anti-inflammatory medications. Like those with

mastocytosis, some patients with mast cell activation syndrome may require higher than normal dosages to control their symptoms (Ref: The Mastocytosis Society Canada 2015). Further information on medications for MCAS can be found in the 2017 paper by Prof Seneviratne et al, entitled Mast Cell Disorders in Ehlers-Danlos Syndrome (see bibliography).

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MCAS extract taken from: Understanding Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorder.

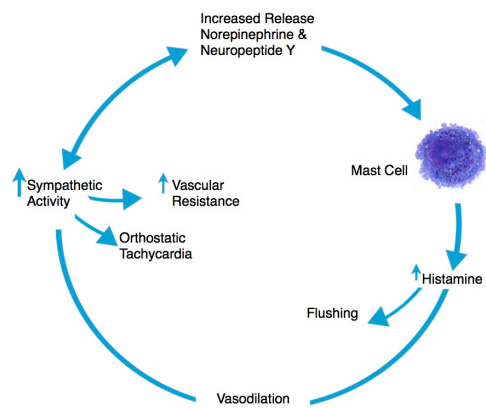
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did not attempt to perform a controlled study, but the observations they made led them to propose that, in some cases of POTs, particularly where patients present with flushing, there may be an underlying association with mast cell activation. They hypothesized that in these cases, activation of mast cell mediators, which are capable of causing constriction or widening of blood vessels, may trigger a 'feedback loop' which results in reflex sympathetic activation; a decrease in volume of blood plasma; norepinephrine release; and thus, orthostatic intolerance.



Recently confirmed evidence of *autoimmunity* in some forms of POTs could also potentially be associated with mast cell activation (Hongliang L. et al 2014). Two types of mast cells are recognised; those from connective tissue, and a distinct set that reside in mucosal tissue. The activities of the latter are dependent on T-cells (De S. 2015) a type of white blood cell best known for their role in autoimmune disorders. Mast cells and T-cells derive along different pathways from a single progenitor cell and may express complementary or overlapping functions (Wedemeyer J. & Galli S.J. 2000 / Seneviratne S. 2016 personal correspondence). A growing body of evidence indicates that mast cells and their mediator release are involved in the exacerbation of many autoimmune disorders (Walker M.E. et al 2012) including multiple sclerosis, rheumatoid arthritis and Sjögren's syndrome (Rozniecki J.J. 1995 / Hueber A.J. et al 2010), with some features of the immune response in autoimmune disorders very much like those of traditional allergic responses (Walker M.E. et al 2012).

The area of autoimmunity in POTs can be a difficult concept. After all, in most patients with EDS/HSD, it is generally attributed to abnormal connective tissue in the blood vessels, which permits veins to swell excessively in response to ordinary hydrostatic pressure, and allows excessive amounts of blood to pool in the patient's abdomen and/or lower limbs when they stand, triggering symptoms [Rowe P.C. 1999 / Bohora S. 2010 / Benarroch E.E. 2012 / Mathias C.J. 2011 / Eccles J. 2015). But POTs can be caused by many different

factors, with different underlying causes in different people. It is, therefore, entirely possible for people with hEDS or HSD to acquire POTs through mechanisms unrelated to their connective tissue abnormalities, in the same way as any member of the general public. In some people, for example, symptoms of POTs start abruptly following trauma, surgery, pregnancy, and also as a secondary condition to viral infection (Soliman K. et al 2010). When POTs is acquired in this way, it is presently felt that is an autoimmune disorder (Vernino S et al 2000 / Grubb B.P. 2008), for which tell-tale serum auto-antibodies have been detected in blood samples (Conner R. 2012).

MCAS, EDS/HSD and POTs are three very complex areas of medicine. Research into any association is likely to be extremely difficult because a person's symptoms can cross so many areas of healthcare and lead to so many complications. However, these apparently unrelated symptoms might, in fact, fit together and they can and should be treated (Hakim A.J. 2016 in person).

Below we will look at the diagnosis of MCAS and its treatment.

Diagnosis of MCAS

MCAS is a diagnosis of exclusion, with primary and secondary mast cell activation disorders (see **Box 2**) as well as idiopathic anaphylaxis usually being ruled out before a diagnosis of MCAS is made (Picard M. et al 2013). It is, therefore, quite common for patients to have undergone multiple extensive medical evaluations to rule out all other causes before finally being given a diagnosis (Akin C. et al 2010).

Unlike rarer, but perhaps better known MCADs such as SM, tests carried out on those with MCAS do not show classic tell tale signs of mast cell proliferation and rarely show the 'significantly' elevated tryptase levels that would traditionally alert most practitioners that they might be dealing with a more widely recognised mast cell activation disorder. Instead, tests are likely to show a normal number of mast cells and only a transient rise (or in some cases, normal levels) of tryptase despite all the physical symptoms of mast cell activation being very much apparent (Afrin L. 2014 / Seneviratne S. et al 2017).

According to Dr Andrew White, in these patients we need to look for other clues that their mast cells are not functioning normally. He says: '*There are many different chemicals that come out of mast cells which can be measured. Substances like histamine,*

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