MAST CELL ACTION

What is Mast Cell Activation Syndrome?

Mast cell activation syndrome (MCAS) is a complex condition that sits within a broad spectrum of disorders associated with oversensitive or inappropriately activated mast cells. MCAS is characterised by the inappropriate or excessive production and/or release of mast cell mediators.[1]

Triggers and Symptoms

MCAS can occur in children and adults, and often has a sudden onset. Triggers of mast cell mediator release vary greatly between patients who suffer from this condition, but commonly include specific foodstuffs, chemicals and fragrances, exercise, stress, infections, mould, or changes in body temperature. It is often difficult for patients to identify their triggers, and the range and severity of triggers may change over time within the same individual, becoming episodic and unpredictable. These inappropriate inflammatory responses result in widespread, multisystem, heterogeneous symptoms including gastric issues, nausea and vomiting, chronic pain, throat swelling, flushing, pruritis and hives, angioedema, bladder conditions, respiratory complications, fatigue, cognitive dysfunction and anaphylaxis.[1–3]

MCAS has been divided into three, non-mutually exclusive, forms:[1]

1. Primary MCAS (also known as clonal MCAS) is caused by underlying monoclonal mast cell disorders such as monoclonal mast cell activation syndrome (MMAS) and mastocytosis (where the patient also meets the diagnostic criteria for MCAS).

   These conditions are defined by the over-proliferation of mast cells and are typically the result of mutations in the KIT gene and/or aberrant expression of CD25 or CD2.

2. Non-clonal secondary MCAS is not the result of an underlying clonal disorder; mast cells are produced at normal or 'near normal' levels. However, in this condition, mast cells are inappropriately activated during immunoglobulin (Ig)E- and/or non-IgE-mediated allergic reactions to typically unharmful triggers.

3. Non-clonal idiopathic MCAS refers to cases where no defined allergic or autoimmune cause has been identified.

Charlotte's Story

As a newborn, Charlotte continuously cried, slept poorly and had dry skin which was irritated, red and swollen on her face. At 4 months old, Charlotte developed hives, vomited frequently in response to feeding and had atypical bowel movements. Her triggers continued to grow in number and severity, leading to hospital admission with low weight, hives and eczema at 6 months old. At 1 year old, Charlotte's lips became swollen after every feed, and she developed a raspy-sounding chest. Charlotte was diagnosed with suspected MCAS at 2 years old.

Though previously described as a rare disease, it appears that this applies only to primary MCAS and that secondary and idiopathic MCAS cases may be more prevalent. For instance, hereditary alpha tryptasemia syndrome (HATS), a recently identified condition shown to overlap substantially with MCAS, is reported to affect 4% of the general population.[4]

1. Akin C. Mast Cell Activation Syndromes. J Allergy Clin Immunol. 2017;140(2):349–355; **2.** Theoharides TC, Tsilioni I, Ren H. Recent Advances in Our Understanding of Mast Cell Activation - or Should it be Mast Cell Mediator Disorders? Expert Rev Clin Immunol. 2019;15(6):639–656; **3.** Afrin LB, Ackerley MB, Bluestein LS, et al. Diagnosis of Mast Cell Activation Syndrome: A Global "Consensus-2". Diagnosis (Berl). 2020;/j/dx.ahead-of-print/dx-2020-0005/dx-2020-0005.xml; **4.** Lyons JJ, Yu X, Hughes JD, et al. Elevated Basal Serum Tryptase Identifies a Multisystem Disorder Associated with Increased TPSAB1 Copy Number. Nat Genet 2016;48(12):1564–9.

Diagnosing MCAS

Due to the wide range of possible symptoms, triggers and potential causes (as well as the need for further research into the disease area), MCAS can be extremely challenging to diagnose. Most MCAS diagnostic processes focus on four key sets of criteria:[1–3]

1. The presence of **typical clinical symptoms across multiple body systems**[4] is the first and most evident indication used to diagnose MCAS.

2. Biochemical evidence of mediator release from mast cells is a crucial step in the diagnostic process. Tryptase serum tests are the most widely recognised and are the only diagnostic mediator tests for MCAS with a specified increase from baseline to use in diagnosis. Serum tryptase should be collected within 4 hours following acute symptom episodes and compared to baseline levels collected 24–48 hours later.[1] A negative tryptase test result does not exclude MCAS, however. **Other mediator tests carried out in the UK** include tests for urinary N-methylhistamine and prostaglandins D_2, DM and $F_{2\alpha}$.[5] When considered alongside other diagnostic evidence, a positive mediator test can increase the confidence of a diagnosis of MCAS.

3. 'Test of treatment' is underpinned by the theory that if a patient responds to a known MCAS treatment, this provides evidence to suggest that the individual has MCAS.

4. Discounting other potential diagnoses is important to ensure an accurate diagnosis of people with MCAS. Conditions which should be ruled out include infectious diseases, irritable bowel syndrome, neoplasms, autoimmune disorders, adrenal insufficiency and cardiovascular disorders such as myocardial infarction.[1]

Additional diagnostic support is provided by the Royal College of General Practitioners, within the **clinical toolkit for Ehlers-Danlos Syndromes**.[6]

When taken together, these four key sets of diagnostic criteria can lead to a confident MCAS diagnosis. However, the trialling of medications using a multi-stage approach, which is often necessary for MCAS cases, can see patients and their families waiting a long time for a definitive diagnosis.

Jensen's Story

From birth, Jensen has struggled with a range of debilitating symptoms across multiple body systems including diarrhoea, urinary incontinence, severe genitourinary pain, hives and sores, anxiety, and syncope.

These reactions occur in response to ever-changing triggers, particularly foodstuffs. Doctors had previously diagnosed Jensen with iron deficiency anaemia, fructose malabsorption, histamine intolerance, chronic idiopathic urticaria and angioedema, with a range of associated treatments which had varying degrees of success.

In 2016, an allergist appointment led to a positive test result for elevated tryptase and a potential MCAS diagnosis. Jensen was later prescribed sodium cromoglicate, ketotifen, cetirizine and fexofenadine; a combination of treatments which stabilised Jensen's mast cells and alleviated many of his symptoms.

Since then, a genetic test has confirmed that Jensen has triplication of the *TPSAB1* gene. Jensen has therefore been diagnosed with hereditary alpha tryptasemia syndrome (HATS).

1. Weiler CR. Mast Cell Activation Syndrome: Tools for Diagnosis and Differential Diagnosis. J Allergy Clin Immunol Pract. 2020;8(2):498–506; **2.** Molderings GJ, Brettner S, Homann J, Afrin LB. Mast Cell Activation Disease: A Concise Practical Guide for Diagnostic Workup and Therapeutic Options. J Hematol Oncol. 2011;4:10; **3.** Valent P, Akin C, Bonadonna P, et al. Proposed Diagnostic Algorithm for Patients with Suspected Mast Cell Activation Syndrome. J Allergy Clin Immunol Pract. 2019;7(4):1125-1133.e1; **4.** The Mast Cell Disease Society. Symptoms of Mast Cell Disease. Available at: https://tmsforacure.org/wp-content/uploads/MCD-Symptoms-Infographic.pdf; **5.** National Health Service, Sheffield Protein Reference Unit and Immunology Department. Test Repertoire. Available at: https://www.immqas.org.uk/pru.asp?CID=1; **6.** Royal College of General Practitioners. The Ehlers-Danlos Syndromes Toolkit. Available at: https://www.rcgp.org.uk/clinical-and-research/resources/toolkits/ehlers-danlos-syndromes-toolkit.aspx.

Managing MCAS

There is currently no cure for MCAS. Therefore, the aim of treatment is to reduce the occurrence and/or severity of symptoms in order to improve the patient's quality of life. This can be achieved using self-management techniques, medicinal products, or a combination of both.

Medical Management

There is currently a wide range of potential treatment options, many of which stabilise mast cells to prevent them from releasing mediators inappropriately (for example, ketotifen and sodium cromoglicate) or mitigate the effects of the mediators they produce (mediator blockers such as H1 or H2 blockers and leukotriene blockers).[1,2]

Due to the vast range of genetic causes, mediators released, triggers and symptoms across individual MCAS cases, it is by no means guaranteed that a treatment that works for one patient will work for another. The response to treatment can be unpredictable, and further complicated by the possibility that some drugs (or the additives or preservatives in them) will in fact trigger adverse reactions in patients.[2] It can often be a slow and multi-stage process for patients to identify a successful treatment regime.

Self-Management

Avoiding triggers is a key part of managing MCAS and relieving symptoms.[1,2] If patients have identified specific triggers of their symptoms – for example, specific foods, medicines or chemicals, exercise or stress – these triggers should be avoided as much as possible to prevent potentially debilitating reactions. Specialist nutritional support is often required for patients to make dietary changes or to undertake an exclusion diet so as to avoid food triggers. However, MCAS triggers are often challenging to identify and new triggers may develop over time. When patients are particularly unstable, the range of triggers and severity of reactions can increase. Further, it is not always possible or practical for people with MCAS to avoid triggers, particularly in public spaces. As a result, self-management of MCAS via trigger avoidance is an extremely challenging and complex task.

With a dedicated multi-stage approach to trial medications, many patients are eventually able to find a treatment regime that works for them.

It is hoped that with further research, it may be possible to personalise medical treatment based on an individual's specific causal MCAS pathway, biochemical mediator profile or range of symptoms.

Suzy's Story

Suzy began experiencing a range of inflammatory symptoms due to the titanium clips left in her body following a gall bladder operation. Her symptoms reduced temporarily upon the removal of these clips. However, the operation to remove the clips led to an umbilical hernia which was repaired using surgical mesh. Suzy's symptoms quickly returned.

Suzy was diagnosed with Ehlers-Danlos Syndrome (EDS), but felt that this did not adequately explain her symptoms. A private immunologist agreed that her symptoms appeared to be consistent with MCAS, and prescribed sodium cromoglicate. Unfortunately, this treatment triggered a serious anaphylactic reaction. This led to the prescription of ketotifen (an alternative mast cell stabiliser) which alleviated some of Suzy's low level symptoms. Suzy's triggers increased in number and severity, and Suzy suffered adverse reactions to the adrenaline which was used to treat her anaphylaxis. She required over two years' treatment with steroids to help stabilise her condition, followed by a higher dose of ketotifen. Suzy's MCAS remains somewhat stable, but she lives a restricted lifestyle in order to avoid potential triggers and she still experiences regular anaphylaxis.

1. Weiler CR, Austen KF, Akin C, et al. AAAAI Mast Cell Disorders Committee Work Group Report: Mast Cell Activation Syndrome (MCAS) Diagnosis and Management. J Allergy Clin Immunol. 2019;144(4):883–896; **2.** Castells M, Butterfield J. Mast Cell Activation Syndrome and Mastocytosis: Initial Treatment Options and Long-Term Management. J Allergy Clin Immunol Pract. 2019;7(4):1097–1106.

How Can We Offer Patients With MCAS Better Support and Medical Care?

The term MCAS was first introduced in 2007, with expert-agreed diagnostic criteria published in 2012.[1] The condition was given an **ICD-10-CM code** in 2016.[2] Whilst MCAS is now well-known to immunologists, more general awareness and acceptance of MCAS as a recognised condition is limited among healthcare professionals, particularly in general practice, where patients are likely to first seek a diagnosis. Awareness in emergency care, for example following an anaphylatic episode, is also low. Even if doctors are aware of MCAS, it can be difficult and time-consuming for patients to get a formal diagnosis. There is limited access to mediator tests on the NHS and people often resort to private practice, where they can pay to access testing.

1 **The introduction of specialist centres to enhance understanding of the presentation of MCAS and common comorbidities would increase confidence in diagnosis, and reduce the time spent testing to eliminate other conditions. With increased understanding, GPs could play a key role in identifying suspected MCAS cases and referring patients for appropriate diagnostic assessment.**

Physicians and patients need to be given the time to undertake a full medical history. Patients with MCAS are too frequently told their symptoms are psychosomatic, even with visible and/or measurable symptoms that meet the internationally agreed diagnostic criteria for MCAS. This lack of recognition can cause **anxiety, fear, depression and feelings of isolation in already unwell patients**, having a devastating impact on families.[3]

2 **There is a need for increased debate, using patient experiences to build up the evidence base for MCAS. For example, establishing a patient registry to capture patient symptoms and their response to different treatments would lead to a better understanding of MCAS and its possible treatments.**

There are cheap and effective treatments available that can reduce symptoms, increase mast cell stability and improve quality of life. However, patients often need to try many different treatments before finding one that works for their specific disease profile.

3 **Even after MCAS has been diagnosed, patients do not have a clearly defined 'home' within the NHS. There is a need for greater access to multidisciplinary teams, where patients with MCAS can receive long-term continuity of care in order to manage their symptoms.**

Lack of co-ordination between specialists can create confusion, leading to multiple appointments across different healthcare services, disjointed treatment and significantly delayed diagnosis (or even misdiagnosis). This leads to increased healthcare costs and overutilisation of restricted NHS resources.

4 **Clear guidelines and care pathways need to be established to improve the delivery of care and access to effective treatment, and to enhance the quality of life for patients with this life-changing condition.**

1. Valent P, Akin C, Arock M, et al. Definitions, Criteria and Global Classification of Mast Cell Disorders with Special Reference to Mast Cell Activation Syndromes: A Consensus Proposal. Int Arch Allergy Immunol. 2012;157(3):215–225; **2.** International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). Available at: https://www.cdc.gov/nchs/icd/icd10cm.htm.; **3.** Jennings SV, Slee VM, Hempstead JB, et al. The Mastocytosis Society (TMS) Mast Cell Activation Syndrome (MCAS) Patient Perceptions Survey. AAAAI Annual Meeting 2018. Available at: https://tmsforacure.org/wp-content/uploads/MCAS.Survey.Poster_The.Mastocytosis.Society.Inc_for.AAAAI_.2019_042219_web.pdf.

Mast Cell Action is a patient support and advocacy charity for MCAS Sufferers.
For further information contact: info@mastcellaction.org
Visit us at: mastcellaction.org

Please visit the 'Resources for Medical Professionals' section of our website for more information on MCAS diagnosis, a range of educational materials, and a bibliography including the latest publications on mast cell activation disorders.

MAST CELL ACTION

Registered Charity Number 1164917