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REVIEW

Mast cell activation syndrome and the link with long COVID

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Abstract

Mast cells are innate immune cells found in connective tissues throughout the body, most prevalent at tissue–environment interfaces. They possess multiple cell-surface receptors which react to various stimuli and, after activation, release many mediators including histamine, heparin, cytokines, prostaglandins, leukotrienes and proteases. In mast cell activation syndrome, excessive amounts of inflammatory mediators are released in response to triggers such as foods, fragrances, stress, exercise, medications or temperature changes. Diagnostic markers may be difficult to assess because of their rapid degradation; these include urinary N-methyl histamine, urinary prostaglandins D_2, DM and $F_{2\alpha}$ and serum tryptase (which is stable) in the UK. Self-management techniques, medications and avoiding triggers may improve quality of life. Treatments include mast cell mediator blockers, mast cell stabilisers and anti-inflammatory agents. 'Long COVID' describes post-COVID-19 syndrome when symptoms persist for more than 12 weeks after initial infection with no alternative diagnosis. Both mast cell activation syndrome and long COVID cause multiple symptoms. It is theorised that COVID-19 infection could lead to exaggeration of existing undiagnosed mast cell activation syndrome, or could activate normal mast cells owing to the persistence of viral particles. Other similarities include the relapse–remission cycle and improvements with similar treatments. Importantly, however, aside from mast cell disorders, long COVID could potentially be attributed to several other conditions.

Key words: Long COVID; Mast cell activation syndrome; Multiple symptomatology; Post-acute sequelae SARS-CoV-2 infection

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Introduction

Mast cell activation syndromes are a heterogeneous group of conditions which sit within a broad spectrum of disorders associated with oversensitive or inappropriately activated mast cells (Figure 1). Mast cell activation syndrome is characterised by widespread, multisystem episodic symptoms. These symptoms result from chronic inappropriate activation of mast cell receptors, rather than increased production of inflammatory mediators (Table 1). Mast cell activation syndrome can occur in both adults and children, and the prevalence may be as high as 17% in some countries (Molderings et al, 2013; Akin, 2017).

This article describes what mast cell activation syndrome is and how it is linked to long COVID.

Mast cells

Mast cells are haematopoietically-derived innate immune cells which reside in connective tissues throughout the body. They are most prevalent at tissue–environment interfaces such as the respiratory epithelium, the length of the gastrointestinal tract, the genitourinary

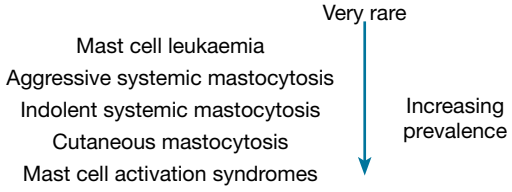

Figure 1. Spectrum of mast cell activation disease. From Afrin and Molderings (2014).

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Table 1. Mast cell receptors and their stimuli

Mast cell receptor	Triggers
High-affinity IgE receptor, FcεRI	■ IgE antibody
Mas-related G protein-coupled receptor X2 (MRGPRX2)	■ Various pharmacological agents (tubocurarine, atracurium, icatibant, ciprofloxacin) ■ Substance P ■ Components of insect venom ■ Antimicrobial peptides ■ Secreted eosinophil products ■ Cationic peptides
IL-33	■ Cell injury ■ Trauma
Pattern recognition receptors	■ 'Danger signals', including microbes
Angiotensin-converting enzyme 2	■ Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

From Dahlin et al (2022)

system and the skin (Afrin and Molderings, 2014). Mast cells have over 200 receptors on their cell surface, which may be excitatory or inhibitory, and which enable them to sense and react to various stimuli (Table 1).

Upon activation by endogenous or exogenous agents, mast cells can release a large number of inflammatory mediators via one of the pathways shown in Figure 2 (Krystel-Whittemore et al, 2016). Some key mediators released by mast cells are histamine, heparin, cytokines, prostaglandins, leukotrienes and several proteases (Afrin and Molderings, 2014). More than 1000 mediators may be expressed by mast cells, resulting in a vastly complex biology.

In mast cell activation syndrome, mast cell-derived inflammatory mediators are released too strongly, too abundantly, or in response to typically harmless triggers such as foods, fragrances, stress, exercise, medications or changes in temperature (Table 2 gives a more comprehensive list of triggers). Inappropriate mediator release results in inappropriate levels of inflammation and a range of symptoms across multiple body systems (Molderings et al, 2013; Akin, 2017). Figure 3 shows some of the symptoms associated with mast cell activation syndrome and the mediators driving these symptoms.

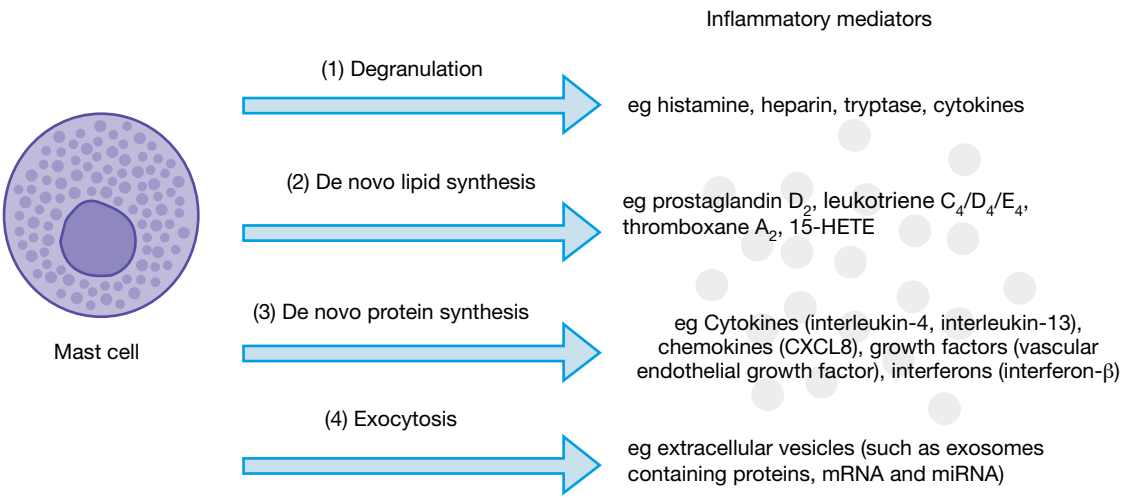

Figure 2. Pathways of mast cell mediator release. Upon activation, mast cells release mediators through one of the following pathways: (1) exocytosis of secretory granules and release of preformed mediators (eg histamine, proteases and heparin) from these granules (known as degranulation); (2) release of newly synthesised lipid mediators (eg prostaglandin D_2 and leukotriene C_4); (3) release of newly synthesised cytokines, chemokines, growth factors and interferons; (4) exocytosis of extracellular vesicles containing proteins, mRNA and miRNA. CXCL8 = C-X-C motif chemokine ligand 8; 15-HETE = 15-hydroxyeicosatetraenoic acid. From Dahlin et al (2022).

Table 2. Triggers for mast cell activation syndrome symptoms
Specific foods (eg high histamine products, gluten, dairy, yeast)
Environmental toxins (pesticides, perfumes, mould, mycotoxins)
Stress
Exercise
Medications (eg local anaesthetics, excipients)
Rapid atmospheric temperature changes
Alcohol
Venoms (eg snake)
Physical stimulation (eg pressure, friction)
Acute or chronic infections (eg Lyme disease, Epstein–Barr virus, tuberculosis)

NB Triggers are unique to the individual; a combination of triggers lowers the threshold for mast cell activation. From Akin (2017), Theoharides et al (2019)

Case examples

Case study 1: a paediatric case

As a newborn, patient X continuously cried, slept poorly and had dry skin which was irritated, red and swollen on her face. At 4 months old, patient X 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, patient X's lips swelled after every feed, and she developed a wheezy-sounding chest. The symptoms worsened over the following year, and patient X was diagnosed with mast cell activation syndrome at 2 years old following abnormally raised levels of urinary N-methyl histamine, and prostaglandins D_2 and $F_{2\alpha}$ on testing. (Her baseline level of mast cell tryptase was normal, demonstrating that serum tryptase levels may not be elevated in all cases of mast cell activation syndrome.)

Case study 2: the treatment journey of a patient with mast cell activation syndrome

Patient Y, a 33-year-old woman, who had been previously well apart from atopic symptoms occurring from childhood, began experiencing a range of inflammatory symptoms when surgeons left titanium clips inside her in error after a gallbladder operation. Her symptoms reduced temporarily following removal of these clips. However, the operation to remove the clips led to an umbilical hernia which was repaired using surgical mesh. Patient Y's symptoms quickly returned.

Patient Y was diagnosed with hypermobile Ehlers–Danlos syndrome, but felt that this did not adequately explain her symptoms. An immunologist agreed that her symptoms appeared to be consistent with mast cell activation syndrome, 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 patient Y's low-level symptoms. Attempts to relieve her other symptoms frequently resulted in additional episodes of life-threatening anaphylaxis. Oral steroids were effective only for a few months.

Patient Y's triggers increased in number and severity, and she suffered adverse reactions to the adrenaline which was used to treat the resultant anaphylaxis. The likely possibility of excipient issues underlying the anaphylactic and non-anaphylactic reactions was considered, and preservative-free adrenaline sourced. Both the titanium clips and the subsequent repair with surgical mesh were likely triggers for this patient's mast cell symptoms, the latter acting as a chronic trigger, making it difficult for medications to gain control over her dysfunctional mast cells.

Treatment with omalizumab is being considered by a specialist allergy clinic for patient Y, to increase the manageability of the symptoms.

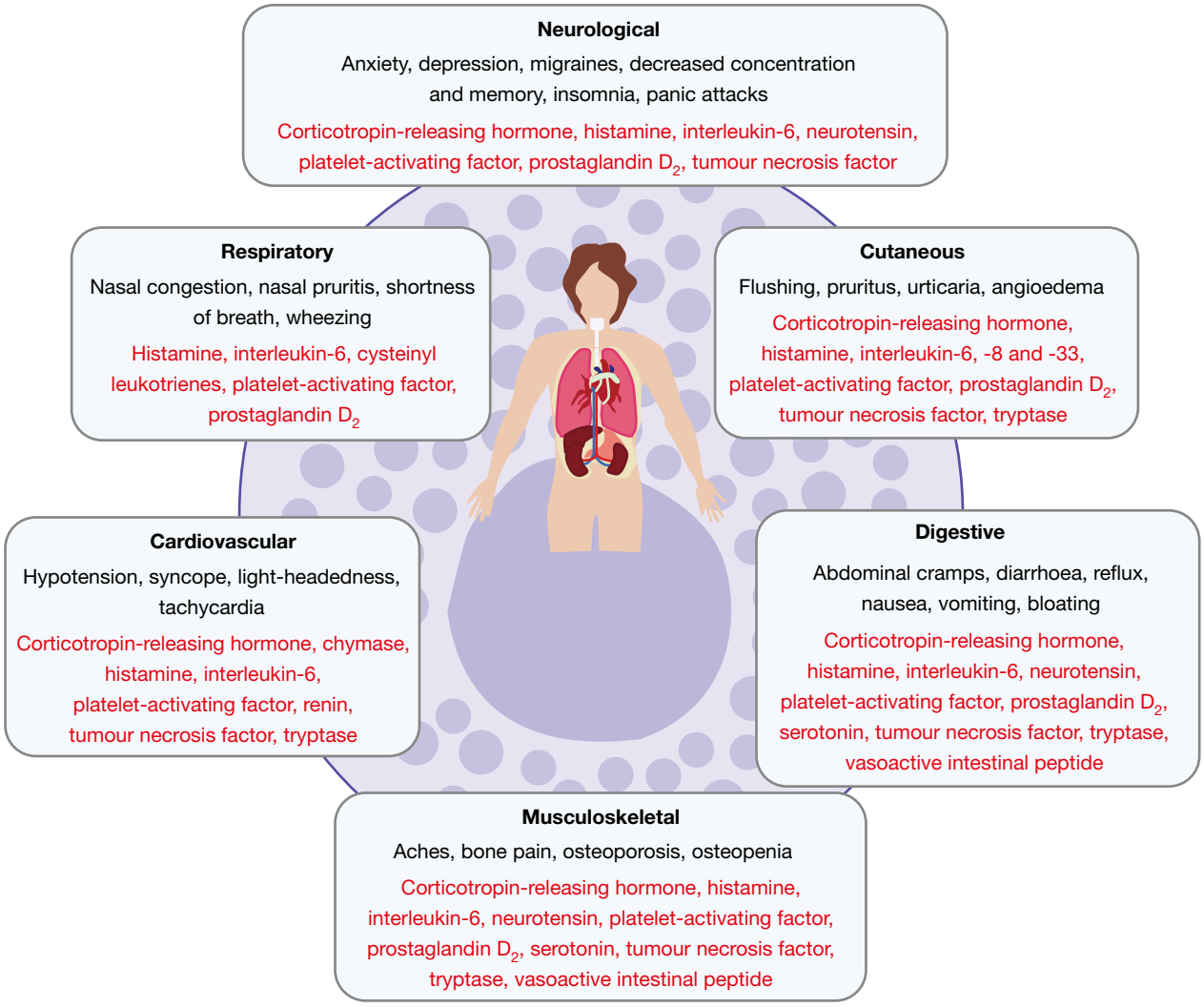

Figure 3. The symptoms associated with mast cell activation syndrome and the mast cell-derived mediators driving these symptoms. From Theoharides et al (2015).

These case studies illustrate that mast cell symptoms may occur from birth in some cases, and that mild mast cell symptoms may pre-date the diagnosis by a number of years. Mast cells may be reacting to excipients in medications, and insertion of foreign substances in the body can act as a chronic trigger.

Mast cell activation syndrome

Mast cell activation syndrome can be classified into different variants (primary, secondary or idiopathic), depending on the condition and its underlying pathology. Primary mast cell activation syndrome is caused by an underlying clonal disorder, such as monoclonal mast cell activation syndrome or mastocytosis (where the diagnostic criteria for mast cell activation syndrome is also fulfilled). Unlike mast cell activation syndrome, mastocytosis is characterised by hyperproliferative mast cells and is typically attributable to mutations in the *KIT* gene, commonly the *KIT* D816V mutation.

In contrast to secondary and idiopathic mast cell activation syndrome, in many cases of primary mast cell activation syndrome, mast cells may aberrantly express CD25 and/or CD2 together with CD117 on their cell surface (Akin, 2017), and/or demonstrate the c-KIT mutation. Secondary mast cell activation syndrome differs from the primary syndrome in that no neoplastic mast cell populations or *KIT* mutations are found. In secondary mast cell activation syndrome, inappropriate mast cell activation occurs as a result of an immunoglobulin (Ig)E-mediated allergy, a hypersensitivity reaction, or another

immunological disorder. Mast cell activation syndrome can manifest as allergic, non-allergic or dystrophic phenomena.

Finally, mast cell activation syndrome is referred to as idiopathic when the diagnostic criteria for mast cell activation syndrome are met but neither an underlying clonal disorder nor a defined allergic cause can be detected at the current time, although specialised research genetic laboratories are able to demonstrate multiple genetic defects in the genes for mast cells (Theoharides et al, 2015).

Tests

As seen in Table 3, diagnostic markers of mast cell activation that are used in the UK include serum tryptase, urinary N-methyl histamine, and the urinary prostaglandins D_2, DM and $F_{2\alpha}$. Ideally two abnormal biochemical values are required for a diagnosis of mast cell activation syndrome (Valent et al, 2019).

Of the mediators listed in Table 3, tryptase is the most specific to mast cells and is often the first mediator measured in those with a suspected mast cell disorder.

Importantly, serum tryptase must be tested within 4 hours after a suspected mast cell activation episode and compared to baseline levels measured 24–48 hours later.

Nevertheless, serum tryptase is not an optimal biomarker for mast cell activation syndrome. The '20% + 2' tryptase formula has not been validated for mast cell activation syndrome and serum tryptase levels are often found to be normal in many cases of non-clonal mast cell activation syndrome (Sala-Cunill et al, 2013).

Demonstrating evidence of elevated mast cell mediator release can be challenging for several reasons. First, mediator levels may only be elevated during a suspected mast cell activation episode and subsequently return to normal levels. It is therefore essential that mediator tests are conducted when symptoms of mast cell activation syndrome are present.

Moreover, because many mast cell mediators are thermolabile, it is crucial that samples are kept chilled in an acid-free bottle throughout collection, storage and transport to avoid degradation and then frozen in the laboratory until analysed (Afrin and Molderings, 2014).

Similarly, as many mast cell mediators have short half-lives, 24-hour urine samples are recommended as spot urine samples may show normal results (British Society for Allergy

Table 3. Mast cell mediators that are validated as markers of mast cell activation and clinically available in the UK

Test	Normal range	Comments
Serum tryptase*	2–14 ug/litre	■ Most specific to mast cells ■ Levels often raised in clonal mast cell activation syndrome but normal in non-clonal mast cell activation syndrome ■ Not raised in all cases of mast cell activation syndrome. Must be measured within 4 hours of a suspected episode and compared with baseline values measured 24–48 hours later
Urinary N-methyl histamine	N-methyl histamine/creatinine ratio (mcg/mmol) <25	■ Fairly specific to mast cells, but also present in basophils ■ May be influenced by diet or bacterial contamination
Urinary prostaglandins (PGD_2 and its metabolites PGDM and $PGF_{2\alpha}$)	Prostaglandin/creatinine ratio (ng/mmol) PGD_2: <825 PGDM: <2300 $PGF_{2\alpha}$: <105	■ Mast cells are the main sources of PGD_2 ■ Positive results for all three prostaglandins are more likely in clonal mast cell activation syndrome ■ A single positive result is more likely in non-clonal mast cell activation syndrome ■ Non-steroidal anti-inflammatory drugs may reduce prostaglandin levels, inflammation may raise (or be raised by) prostaglandin levels ■ Ovulation, menstruation, polycystic ovary syndrome and endometriosis may raise $PGF_{2\alpha}$

**Serum tryptase levels are elevated in some severe cases of anaphylaxis but often remain normal in patients with mild or moderate anaphylaxis. NB If serum tryptase is >8 ng/ml, check for hereditary alpha tryptasaemia. From Akin et al (2010), Sala-Cunill et al (2013), Butterfield and Weiler (2020), British Society for Allergy and Clinical Immunology (2021)*

and Clinical Immunology, 2021). Importantly, no single mediator test is definitive. A single positive test result does not indicate that a person definitely has mast cell activation syndrome, and a single negative test result is insufficient to rule out mast cell activation syndrome. Mediator tests can only provide reasonable confidence in a diagnosis of mast cell activation syndrome when other diagnostic criteria are also fulfilled (Table 4).

Managing mast cell activation syndrome

Although there is currently no permanent cure for mast cell activation syndrome, self-management techniques and medications can improve a patient's quality of life by reducing the occurrence and/or the severity of symptoms. Avoiding triggers which may provoke potentially debilitating reactions is a key aspect of self-managing the condition.

However, trigger avoidance can be a challenging task as triggers may be difficult to pinpoint and may change over time. Moreover, it may not be practical or possible for patients with mast cell activation syndrome to avoid certain triggers, particularly in public (Molderings et al, 2016).

As seen in Table 5, there are several treatment options for mast cell activation syndrome. Many of these drugs either stabilise mast cells to inhibit the release of mediators (eg sodium cromoglicate or ketotifen), or mitigate the effects of mast cell mediators (eg antihistamines, anti-leukotrienes and anti-prostaglandins). Drugs which reduce inflammation (eg corticosteroids and immunosuppressives) may also be used.

Drugs that block mast cell activation, such as antibody therapies and tyrosine kinase inhibitors, are infrequently used for managing mast cell activation syndrome (Molderings et al, 2016). Patients with mast cell activation syndrome are advised to take mast cell mediator blockers (eg antihistamines) prophylactically throughout life and allergy-prone patients are advised to carry two (or more) adrenaline autoinjectors in case of an emergency.

Patients with mast cell activation syndrome often require multiple different therapies at once, and identifying a successful medication regimen for an individual can be a complicated and lengthy process. Owing to the variation in triggers, mediator release and symptoms among patients with mast cell activation syndrome, medication that may be effective in one individual may be ineffective in another. Response to treatment is unpredictable and further complicated by the fact that drugs (or their excipients) may act as triggers for some patients. With further research, it is hoped that treatments can be personalised based on an individual's triggers, symptoms or biochemical mediator profile. Recent shortages of mast cell stabilisers (Table 5) have resulted in deterioration of symptoms.

Long COVID and mast cell activation syndrome

The terms 'long COVID', 'long-hauler syndrome' and PASC (post-acute sequelae severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection) are the terms most commonly used to describe post-COVID-19 syndrome in the UK and USA. This refers to symptoms consistent with COVID-19 which develop and remain for more than 12 weeks after initial infection and cannot be explained by any alternative diagnosis (National Institute for Health and Care Excellence, 2020).

The majority of long COVID symptoms are also symptoms of mast cell activation syndrome, leading many to consider that there may be a link between them. Research by Weinstock et al (2021) found that symptoms experienced by patients with mast cell activation syndrome and those with long COVID were virtually identical and theorised

Table 4. Key diagnostic criteria for mast cell activation syndrome

The presence of typical clinical mast cell activation syndrome symptoms across multiple body systems
Evidence of raised levels of mast cell mediators (Table 3)
Substantial systemic response to inhibitors of mast cell activation or inhibitors of mast cell mediator production or action (Table 5)
Exclusion of other potential diagnoses such as neuroendocrine tumours or cortisol insufficiency

From Valent et al (2019); Afrin et al (2021)

Table 5. Drugs used to treat mast cell activation syndrome

Treatment	Example	Mechanism
Mast cell mediator blockers	H_1 antihistamines, eg fexofenadine, and H_2 antihistamines, eg famotidine, as well as H_3 and H_4 blockers	Mitigate the effects of histamine through competitive antagonism at H_1, H_2, H_3 or H_4 receptors
Mast cell stabilisers	■ Ketotifen ■ Sodium cromoglicate ■ Quercetin ■ Luteolin	Stabilise mast cells to inhibit the release of inflammatory mediators from mast cells
Anti-leukotrienes	Montelukast	Reduce leukotriene levels by inhibiting different levels of the lipoxygenase pathway, which is involved in the formation of leukotrienes from arachidonic acid
Anti-prostaglandins or anti-inflammatory	■ Aspirin ■ Ibuprofen ■ Naproxen ■ Low dose naltrexone	Reduce prostaglandin levels by inhibiting cyclooxygenase which is required to convert arachidonic acid into prostaglandins
Antibody therapies	Omalizumab	Prevents mast cell activation by inhibiting the binding of IgE to the high affinity IgE receptor (FcεRI) on the surface of mast cells
Corticosteroids	Prednisolone	Prednisolone decreases inflammation via suppression of the migration of leukocytes and reversal of increased capillary permeability
Immunosuppressive	Ciclosporin	Inhibits the production of cytokines involved in the regulation of T-cell activation (particularly interleukin-2)
Tyrosine kinase inhibitors	Imatinib	Imatinib (infrequently used) may inhibit the growth-promoting role of wild type ckit or block an oncogenic kinase
Emergency medications	Adrenaline or adrenaline autoinjectors (eg EpiPens)	Reduce symptoms of anaphylaxis (eg hypotension) through causing vasoconstriction
Vitamins and minerals	■ Vitamin C ■ Vitamin D ■ Magnesium	Vitamin C breaks down histamine and contributes to mast cell stabilisation Vitamin D contributes to mast cell stabilisation Magnesium controls mast cell division and histamine production

that the increase in mast cell activation induced by COVID-19 infection may underlie part of the pathophysiology of long COVID (Figure 4).

Literature exploring connections between mast cell activation syndrome and long COVID all touches upon the pathophysiological similarities. As previously mentioned, mast cells become activated by viruses such as COVID-19 and react by releasing chemical and pro-inflammatory mediators to protect the body. Mast cell activation syndrome is characterised by a permanent escalation in baseline levels of mast cell dysfunction after a particular major stressor. Thus, infection with SARS-CoV-2 and resulting COVID-19 illness can be considered a triggering event for mast cell activation syndrome. Generally, after COVID-19 infection has receded, mast cell activity will return to normal baseline levels. However, this is not the case with long COVID patients, whose mast cells continue increased activation to abnormal levels, as seen in people with mast cell activation syndrome (Afrin et al, 2020).

This abnormal activation of mast cells causes a myriad of symptoms experienced by both long COVID and mast cell activation syndrome patients. Thus, it has been theorised and accepted by some that COVID infection can lead to exaggeration of existing and underlying (but undiagnosed) mast cell disorders.

Another aspect raising suspicions of a link is the relapse–remission cycle experienced by many people suffering from long COVID. Davis et al (2021) found 85.9% of 3762 people

from 56 countries taking part in their research experienced this. This is of interest because some patients with mast cell activation syndrome (particularly those suffering from idiopathic mast cell activation syndrome) experience periods of 'flares' interspersed with periods of remissions. Mast cell activation syndrome flares and symptoms are typically triggered by certain provoking factors, with each patient having their own unique set of triggers. In the study by Davis et al (2021), long COVID patients reported that foods high in histamines, lack of sleep, cold air, over-exertion, fragrances and smoke would trigger their symptoms. These triggers are also commonly associated with mast cell activation syndrome.

It has been proposed that medications acting against mast cells, as well as mast cell stabilisers, could be used to treat symptoms of long COVID. These treatments are being tested in clinical trials, and doctors are already treating patients with long COVID with medications typically used by mast cell activation syndrome patients, such as H_1 and H_2 antihistamine receptor antagonists (Davis et al, 2021). There have also been reported improvements in long COVID patients after treatment with sodium cromoglicate, quercetin and luteolin, low dose naltrexone, montelukast, and vitamins C and D (Weinstock et al, 2021). As can be seen from Table 4 and Figure 4, there are multiple overlapping symptoms which fulfil the criteria for mast cell activation syndrome. Therefore, it would make sense for a diagnosis of mast cell activation syndrome to be considered for long COVID patients meeting these criteria.

It is becoming increasingly clear that there is a relationship between long COVID and mast cell activation syndrome; in the capacity that SARS-CoV-2 triggers mast cell responses which exaggerate pre-existing mast cell activation syndrome in patients. The reality of mast cell activation syndrome, as known by patients themselves, is that research into the condition, as well as understanding and awareness among medical professionals, is severely lacking. This has a knock-on effect for long COVID patients who are suffering because of a likely underlying mast cell disorder.

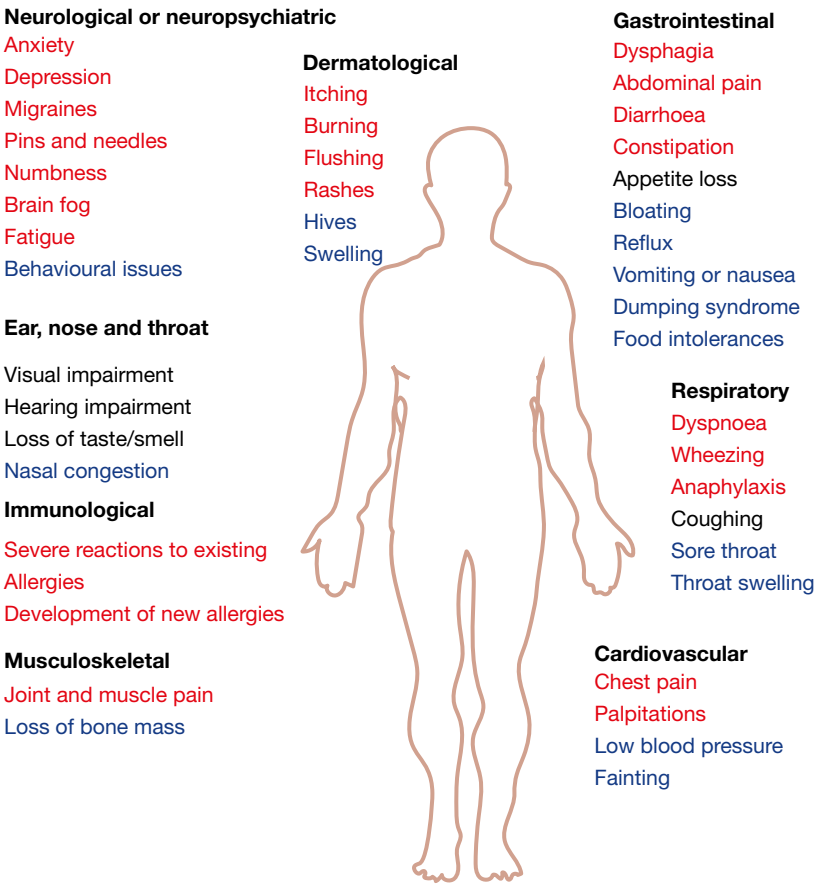

Figure 4. Long COVID symptoms. Those highlighted in red are shared with mast cell activation syndrome, and those highlighted in blue are general symptoms of mast cell activation syndrome.

Key points

- Mast cells are innate immune tissue cells lining tissue–environment interfaces.
- They have multiple cell-surface receptors and may release large number of mediators.
- Mast cell activation syndrome is heterogeneous and results in multiple system symptomatology.
- Diagnosis of mast cell activation syndrome may be difficult as most mediators degrade rapidly.
- Long COVID is a syndrome in which symptoms persist for more than 12 weeks after COVID-19 infection, and many symptoms overlap with mast cell activation syndrome.
- Similarities between mast cell activation syndrome and long COVID include the relapse–remission pattern and improvements with similar medications in both.
- Other underlying pathologies may also be associated with long COVID rather than being solely attributed to mast cell activation syndrome.
- Similar laboratory abnormalities occur in patients with mast cell activation syndrome and those with long COVID.

However, it is important to keep in mind that other conditions could be connected to long COVID, rather than solely attributing long COVID to mast cell disorders. For example, another condition that is being questioned as to its link with long COVID is multisystem inflammatory syndrome. This is most commonly seen in children who have experienced COVID-19, whereas in adults it is rare. While multisystem inflammatory syndrome in children has been linked to serious inflammation caused by severe COVID-19, multisystem inflammatory syndrome in adults is believed to be associated with asymptomatic COVID-19 carriers and is generally found in adults 4–6 weeks after infection. In adults this condition has been found to cause diffuse maculopapular or erythematous rash, typically across the upper body. Other symptoms include dyspnoea, vomiting and diarrhoea, myalgia, and high fever (Yao et al, 2021). Because so little is understood about this condition, there are currently no existing guidelines on management or treatment, other than findings from Yao et al (2021) describing the success of corticosteroid therapy. Most children with multisystem inflammatory syndrome will recover eventually, but some will rapidly deteriorate to a life-threatening level (Mayo Clinic Staff, 2021).

Conclusions

Mast cells are innate immune cells lining the entrances, exits and the body's cavities, and inappropriate release of inflammatory substances secondary to a large number of variable triggers results in a multisystem disorder. There is evidence that in some cases of long COVID, all or some of the symptoms replicate those of mast cell activation syndrome and respond to similar treatments.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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