



Research Summary: MCAS #1

As featured in Dr. Kenny Mittelstadt's video:
Why MCAS Symptoms Keep Getting Misread
Date of Publication: 06/18/2026

Research Context:

For many people living with Mast Cell Activation Syndrome, the path to understanding what is happening in their body has been measured not in months but in decades. This week's topic explores why MCAS so consistently goes unrecognized, what the research shows about how long that process takes, and what a more recent body of evidence suggests about the connection between COVID-19 and immune threshold shifts.

The studies below help explain why multi-system reactivity gets misread as separate problems, and what it looks like when the right questions are finally asked.

Key Findings from the Research:

Study 1 (PMID 28262205):

In the first systematic look at a large group of people with confirmed MCAS, researchers followed 413 patients and found that symptoms typically began in childhood, with a median onset age of 9, while diagnosis did not come until a median age of 49. That gap, a median of 30 years between first symptoms and accurate diagnosis, tells you something important about how the standard model reads this condition. Patients averaged 20 distinct symptoms and 11 comorbidities, which reflects just how broadly mast cell activation affects the body across systems. Importantly, the most useful diagnostic markers were heparin, prostaglandin D2, histamine, and chromogranin A. These are not part of a routine workup. Standard allergy panels and basic labs, the ones most people encounter in those 30 years, were not the tools that brought the pattern into focus.

Study 2 (PMID 34563706):

Researchers compared three groups: 136 people with long COVID, 136 healthy controls who had never had COVID-19, and 80 people with confirmed MCAS. Before infection, the long COVID group and the healthy controls had virtually identical mast cell activation symptom profiles. After COVID, the long COVID group's symptom scores were virtually indistinguishable from those of untreated MCAS patients across multiple measures of both symptom presence and severity. This was not a gradual drift toward overlap. It was a near-complete match. The researchers interpreted this as evidence that SARS-CoV-2 may trigger or unmask mast cell dysregulation in a meaningful subset of people, shifting a system that was previously functioning into a state that looks, from the outside, just like MCAS.

Study 3 (PMID 34820848):

This preliminary letter in Allergy looked directly at blood-based immune markers in people with persistent post-COVID symptoms compared to people who recovered without complications. Researchers found that two mast cell-derived proteins, active tryptase and carboxypeptidase A3, were significantly higher in the long COVID group than in those who recovered fully. This is a small sample and should be read as an early mechanistic signal rather than a definitive finding, and the script acknowledges that evidence tier. What it adds is a biological layer beneath the symptom pattern the prior study described: the people who stayed sick showed measurably different immune activity in their blood, and that difference was trackable, even if it is not yet part of standard post-COVID care.



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Functional Medicine Connections:

Here is how these pieces fit together. Standard allergy testing looks for one specific pathway of immune reactivity, the IgE-mediated response that drives classic allergies. Mast cells can fire through entirely different pathways, which means a person can test negative for allergies while still experiencing significant mast cell-driven symptoms. That is part of why 30 years can pass before someone gets an accurate picture.

What the long COVID research adds is a different kind of context. The immune system does not reset cleanly after every infection. In some people, a viral event appears to lower the threshold at which mast cells respond, so inputs that were previously tolerated are now enough to cross the activation line. The body has not changed what it is doing. It has changed where it sets the trigger.

This connects to how functional medicine reads these patterns differently. Rather than evaluating each symptom at the organ level, the investigation follows the load: what is the cumulative burden on the system, what shifted and when, and what does the full picture suggest about where the threshold moved. Tryptase measured at a quiet moment does not tell you what happened during the last flare. That is the interpretation gap where many people fall through.

Practical Reflections & Takeaways:

If your symptoms seem to shift unpredictably, worsening in certain environments or after certain life events without a clear single trigger, what does that pattern look like when you map it across time? Is there a threshold event, a move, an illness, a period of prolonged stress, where the overall load changed?

If your labs have come back normal but your experience has not, what would it mean for you to hold both of those things as true at the same time, that the tests were accurate for what they measured and that they may not have been measuring the right things?

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