

KEY DIAGNOSTIC CRITERIA ^{1,2}

1. The presence of typical clinical MCAS symptoms across multiple body systems.
2. Evidence of raised levels of mast cell mediators (see "Mediator Tests").
3. Substantial systemic response to inhibitors of mast cell activation or inhibitors of mast cell mediator production or action.
4. Exclusion of other potential diagnoses.



Scan for more on diagnosis

MEDIATOR TESTS ^{3, 4, 5, 6, 7, 8}

Test	Normal Range	Comments
Serum tryptase	2 to 14 ug/L	<ul style="list-style-type: none"> • Most specific to mast cells • Often raised in clonal MCAS but normal in non-clonal MCAS • Must be measured within 4 hours of a suspected episode and compared with baseline values measured 24 to 48 hours later • An increase of at least 20% over the individual's baseline plus 2ng/ml may indicate anaphylaxis*
Urinary N-methyl histamine	<u>NMH/ creatinine ratio (mcg/mmol)</u> <25	<ul style="list-style-type: none"> • Fairly specific to mast cells, however also present in basophils • No validated diagnostic threshold • May be influenced by diet or bacterial contamination
Urinary Prostaglandins (PGD2 and its metabolites PGDM and PGF2α)	<u>PG/ creatinine ratio (ng/mmol)</u> PGD2: <825 PGDM: <2300 PGF2α: <105	<ul style="list-style-type: none"> • Not specific - not recommended as a single marker of mast cell activation • No validated diagnostic threshold • Positive results for all three PGs is more likely in clonal MCAS • A single positive result is more likely in non-clonal MCAS • NSAIDs may reduce PGs, inflammation may raise PGs • Ovulation, menstruation, PCOS and endometriosis may raise PGF2α

*The "20% + 2" tryptase formula has not been validated for MCAS. Although the formula may be useful for anaphylaxis, it is not optimal. Tryptase elevation correlates with the severity of anaphylaxis; serum tryptase is elevated in some severe anaphylaxis cases but often remains normal in patients with mild or moderate anaphylaxis. N.B. If serum tryptase is >8 ng/ml, check for hereditary alpha tryptasemia.

IMPORTANT INFORMATION ^{6, 9}

Testing Protocol



- 24-hour urine samples are recommended as mast cell mediators with short half lives may show normal results in spot urine samples.
- Sample collection starts after the first urination of day 1 and includes the first urination of day 2.



- As many mast cell mediators are thermolabile, samples must be kept chilled throughout collection, storage and transport and frozen in the lab.
- The container used for sample collection must be chilled prior to sampling.
- Each sample must be collected in a different container and then chilled.



- Multiple tests are often conducted; ideally two abnormal biochemical values are required to diagnose MCAS.
- Urine samples must be collected in an acid free container.

IMPORTANT INFORMATION ⁶

Analysis



- A single positive result does not say that a person certainly has MCAS, and a single negative result is insufficient to rule out MCAS. When considered alongside other evidence, these mediator tests can provide reasonable confidence in a diagnosis.



- MCAS patients may not have raised mast cell mediator levels unless they are symptomatic.

MEDIATORS AND SYMPTOMS ^{6, 10}

Symptoms	Mediators
Cardiovascular Hypotension, syncope, light-headedness, tachycardia	CHR, chymase, histamine, interleukin-6, PAF, renin, TNF, tryptase
Cutaneous Flushing, pruritus, urticaria, angioedema	CRH, histamine, interleukin-6, 8, 33, PAF, TNF, tryptase
Digestive Abdominal cramps, diarrhoea, esophageal reflux, nausea and vomiting	CHR, histamine, interleukin-6, neurotensin, PAF, PGD2, serotonin, TNF, tryptase, VIP
Musculoskeletal Aches, bone pain, osteopenia, osteoporosis	Interleukin-6, PGD2, RANKI, TNF, tryptase
Neurologic Anxiety, depression, decreased concentration and memory, insomnia, migraines	CRH, histamine, interleukin-6, neurotensin, PAF, PGD2, TNF
Respiratory Nasal congestion, nasal pruritus, shortness of breath, throat swelling, wheezing	Histamine, interleukin-6, CysLTs, PAF, PGD2
Systemic Fatigue, generalised malaise, weight loss	CRH, histamine, interleukin-6, TNF

OTHER MEDIATOR TESTS ^{5, 11}

Test	Comments
Leukotriene E4	<ul style="list-style-type: none"> • Not available in the UK.
Carboxypeptidase	<ul style="list-style-type: none"> • Elevated levels may indicate anaphylaxis. • May reduce false negatives by picking up serum tryptase-negative cases.

- Although mast cells release a number of mediators (as seen in the "Mediators and Symptoms" table on the left), only a small proportion of these mediators are used as diagnostic biomarkers for MCAS.
- The mediators involved, symptoms experienced, and tests required to diagnose MCAS vary from individual to individual. This heterogeneity is also seen in mastocytosis, a similar mast cell disorder.
- It is hoped that with further research, it may be possible to personalise tests and medical treatment based on one's biochemical mediator profile or range of symptoms.

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[MCAS-associated symptoms and the mast cell mediators driving these symptoms. Information taken from Theoharides et al. 2015.]

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