

Neuropsychiatric symptoms in MCAS and Histamine Intolerance

For Mast Cell Action - April 2026

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Psychoneuroimmunoendocrinology

- Psych- affecting the brain/mood/emotions
- Neuro- by direct affect on the nerves
- Immuno- the cells of the immune system are playing a part
- Endocrin- a hormonal contribution

-ology- all of the above

An Under-recognised part of MCAS and HI- and overall in Medicine

Mast cell activity and their mediators can affect a patient's mood

Histamine flares can affect mood

Mood can be affected on a spectrum- from anxiety and irritability to suicidal ideation

Mast cells are cited on the borders of nerves and vessels meaning their mediators can have prompt neurological actions and can be transported round the body promptly

How do I know it is real? Because I see it all the time in practice

- Patients present with:
 - Anxiety
 - Irritability
 - Depressed mood
 - Changeable tolerance to the same set of circumstances
 - Suicidal consideration - usually quite distinct from the suicidal ideation of organic depression
- Their mental state is changeable- 3 days of low, then better
- Mental state changes with triggers- high histamine foods, chemical exposures, infection
- Their mood symptoms improve with Mast Cell directed treatments

The World is waking up to this phenomenon:

Psychiatry Online - February 2026 - Erica Burger DO

Mast cell activation syndrome (MCAS) is an underrecognized condition that may drive neuropsychiatric symptoms such as anxiety, “cognitive fog,” and paradoxical medication responses (Theoharides, 2022; Schofield & Afrin, 2019).

Patients may also report coexisting postural orthostatic tachycardia syndrome (POTS), Ehlers-Danlos syndrome (EDS), irritable bowel syndrome (IBS), or environmental sensitivities (Afrin, et al., 2017; Seneviratne, et al., 2017).

It is an imperative in psychiatry—particularly in consultation-liaison settings—to first seek an explanation of psychiatric symptoms in general medical illness. Recognizing neuroimmune contributors like MCAS can shift clinical framing and reduce harm.

Schofield JR, Afrin LB: [Recognition and management of medication excipient reactivity in patients with mast cell activation syndrome](#). Am J Med Sci 2019;357(6):507-511.

Seneviratne SL, Maitland A, Afrin LB: [Mast cell disorders in Ehlers-Danlos syndrome](#). Am J Med Genet C Semin Med Genet 2017;175(1):226-236.

Brain Mast Cells, Neuroinflammation and Cognition

Mast cells are activated by IgE and non-IgE stimuli including neuropeptides resulting in release of individual or numerous biologically active mediators that include biogenic amines, chemokines, cytokines, hormones, and neurotransmitters.

Unique among the mast cells are those found in the brain, especially in the thalamus and hypothalamus, even though IgE does not cross the blood-brain barrier (BBB) and the brain does not get allergic reactions.

Brain mast cells act as the ‘immune gate to the brain’ by controlling the permeability of the BBB, but also serve as a “master neuroimmune regulator” of homeostasis, cognition and behavior via direct communication with microglia and neurons.

Brain mast cells can participate in neuroinflammation and in the pathogenesis of a number of neuropsychiatric disorders such as Alzheimer’s disease (AD), Autism spectrum disorder (ASD) and Long COVID syndrome.

Inhibition of brain mast cell hyperreactivity is necessary in order to prevent or treat neuroinflammatory and neurodegenerative disorders and could be accomplished with liposomal formulations of certain natural flavonoids, especially luteolin.

Mast cell activation disease: An underappreciated cause of neurologic and psychiatric symptoms and diseases

Neurologists and psychiatrists frequently encounter patients whose central and/or peripheral neurologic and/or psychiatric symptoms (NPS) are accompanied by other symptoms for which investigation finds no unifying cause and for which empiric therapy often provides little to no benefit.

Systemic mast cell activation disease (MCAD) has rarely been considered in the differential diagnosis in such situations.

MC mediators and their complex patterns of release, engender complex, nebulous presentations of chronic and acute illness best characterized as multisystem polymorbidity of generally inflammatory \pm allergic themes – including very wide arrays of central and peripheral NPS.

Significantly helpful treatment – including for neuropsychiatric issues – usually can be identified once MCAD is accurately diagnosed.

Since MCAD patients often present NPS, neurologists and psychiatrists have the opportunity, in recognizing the diagnostic possibility of MCAD, to short-circuit the often decades-long delay in establishing the correct diagnosis required to identify optimal therapy.

Afrin LB, Pöhlau D, Raithel M, et al.: Mast cell activation disease: an underappreciated cause of neurologic and psychiatric symptoms and diseases. *Brain Behav Immun* 2015;50:314-321

Neuropsychiatric Manifestations of Mast Cell Activation Syndrome and Response to Mast-Cell-Directed Treatment: A Case Series

A case series of eight patients with significant neuropsychiatric disorders that were often refractory to standard medical therapeutics.

- Five patients had depression
- Five had generalized anxiety disorder
- Four had panic disorder

Other psychiatric disorders included attention-deficit hyperactivity disorder, obsessive compulsive disorder, phobias, and bipolar disorder.

All eight patients were subsequently diagnosed with mast cell activation syndrome

Six had comorbid autonomic disorders, the most common being postural orthostatic tachycardia syndrome; and four had hypermobile Ehlers-Danlos syndrome

All patients experienced significant improvements regarding neuropsychiatric and multisystemic symptoms after mast-cell-directed therapy.

A case series of diamine oxidase deficiency misdiagnosed as anxiety or panic attacks in patients with tachycardia

Diamine oxidase (DAO) deficiency, a key marker of histamine intolerance (HIT), often mimics anxiety or panic disorders, leading to a misdiagnoses and delayed treatment.

5 cases: Female (aged 25–54) with chronic, non-specific symptoms, including

Palpitations, nasal congestion, and gastrointestinal disturbances, initially attributed to the anxiety. Serum DAO levels below 10 IU/ mL confirmed HIT in all cases.

Treatment with a low-histamine diet and DAO supplementation significantly improved symptoms, highlighting the importance of considering HIT in such cases. One patient experienced recurrence after discontinuing treatment, emphasizing the need for long term management. Genetic testing in one case revealed variants linked to reduced DAO activity, suggesting a potential genetic predisposition.

In Summary

It is real

We need to recognise it

We need to help

Therapies that can be considered:

- H1A/ H2A/ Ketotifen
- PureLut/ Neuroprotek
- Vitamin D, Vitamin C
- Mirtazapine

MCAS and ADHD and ADD

A paper from Italy proposes that Mast Cells have a role in developmental neuropsychiatric disorders.

Dr Theo Theoharides has published many papers to this effect - refer to MastCellMaster.com

This podcast from a developmental Paediatrician in the US supports that supporting mast cells improves childrens' neurodevelopmental symptom burden

<https://podcasts.apple.com/gb/podcast/mcas-in-developmental-and-behavioral-pediatrics-with/id1717106678?i=1000703742284>