Refractory depression, chronic anxiety, PTSD:

what if it were also inflammatory?

Mast cells in the brain

Mast cells are present in the brain — particularly in the hypothalamus, hippocampus, substantia nigra and meninges. They are the only leucocytes to reside in brain tissue under normal conditions, positioned at the interface of vessels and neurons. Upon activation, they release neuroactive mediators: histamine (direct neuromodulator), tryptase (PAR-2 neuron activation), TNF-alpha, IL-6, nerve growth factor — creating neuroinflammation whose behavioural and psychiatric consequences are now increasingly well documented.

Refractory depression and immune signature

A significant subgroup of antidepressant-resistant depressions presents a systemic inflammatory signature — elevated CRP, elevated IL-6, altered kynurenine/tryptophan ratio. In the PMCHS terrain, this low-grade inflammation is partly mast cell-driven: chronic degranulation sustains the IDO (indoleamine 2,3-dioxygenase) axis, diverting tryptophan from serotonin synthesis towards kynurenine production — a neuroexcitatory metabolite.

“ Depression that does not respond to classical serotonergic antidepressants, associated with fatigue, diffuse pain and digestive disorders, should raise suspicion of a mast cell neuroinflammatory component in a PMCHS terrain. ”

The LC/noradrenergic axis (locus coeruleus) is also involved: peri-LC mast cells activate the noradrenergic stress response, maintaining a chronic state of alert that overlaps with depression and complicates treatment response.

Chronic anxiety and mast cell hypervigilance

The amygdala — the fear and alert processing centre — is richly vascularised and surrounded by mast cells. In the PMCHS terrain, NR3C1 methylation induced by early adversity reprogrammes the amygdala towards a chronic hypervigilance mode, lowering the threat detection threshold. This hypersensitive amygdala in turn activates the HPA axis and mast cell degranulation — creating a self-sustaining loop between anxiety, inflammation and mast cell reactivity.

'Causeless' anxiety, panic attacks triggered by minor sensory stimuli, hyperreactivity to noise or light — these presentations are consistent with amygdala sensitisation of mast cell origin.

PTSD and threat memory

Post-traumatic stress involves abnormal memory consolidation of threatening events in the hippocampus and amygdala. Mast cells play a role in this process: during the traumatic event, massive degranulation releases NGF (nerve growth factor) that potentiates the synaptic plasticity of fear memory. In the PMCHS terrain, the degranulation threshold being lowered, events of lesser intensity can be sufficient to engrave a traumatic memory — explaining the particular vulnerability to PTSD observed in PMCHS profiles.

This perspective opens a therapeutic avenue: preventive mast cell stabilisation during periods of intense stress could reduce traumatic consolidation. Preliminary work on ketamine and mast cell stabilisers in PTSD points in this direction.

The IDO/kynurenine axis: when serotonin runs out of precursor

In the PMCHS terrain, depression resistant to serotonergic antidepressants (SSRIs) is often explained not by a dysfunction of 5-HT receptors, but by a depletion of the precursor: tryptophan. Chronic mast cell inflammation activates the IDO enzyme (indoleamine 2,3-dioxygenase), which diverts tryptophan towards kynurenine production — a neuroexcitatory metabolite involved in anxiety, cerebral inflammation and neurotoxicity — at the expense of serotonin synthesis.

The result: less tryptophan available for serotonin production, a brain deficient in serotonin despite functional receptors, and SSRIs that cannot find their substrate. This mechanism is worsened by tryptophan-rich foods consumed without complex carbohydrates (which facilitate tryptophan crossing the blood-brain barrier), by alcohol, and by glutamate spikes that directly stimulate intestinal enterochromaffin cells — which produce 95% of the body's serotonin.

Practical implications: in PMCHS depressions resistant to SSRIs, explore the urinary or plasma kynurenine/tryptophan ratio, reduce pro-inflammatory foods that feed the IDO pathway, and ensure adequate intake of serotonin synthesis cofactors: **magnesium, zinc, vitamin B6 and iron** — frequently deficient in the PMCHS terrain.

What this means in practice

- Mention the PMCHS/MCAS terrain to your psychiatrist or psychologist: **mast cell neuroinflammation may explain resistance** to standard treatments.
- Request a basic inflammatory panel: **hsCRP, IL-6, FBC**. A chronically elevated CRP without infectious cause is a signal.
- **Mast cell stabilisation** (quercetin, luteolin, H1 antihistamines) may improve the anxiety-depressive picture by addressing the underlying inflammatory component.
- **Sophrology, heart rate coherence and somatic approaches** act on the amygdala-HPA axis and reduce stress-induced mast cell degranulation — complementary to pharmacological treatment.
