

Notes on Mast Cell Activation Disorder and ME/CFS

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Few would dispute that the immunology of ME/CFS is complex and that the findings presented in the literature sometimes appear to be inconsistent.

Whilst much has been published about one sub-group of ME/CFS patients with a low T4 (CD4/helper cell) and a high T8 (CD8/suppressor cell) ratio, not as much seems to have been published about people with ME/CFS who have the opposite T-cell ratio (ie. a high T-cell helper/low suppressor T-cell ratio).

Such an increased T4:T8 ratio resulting in a relative suppressor cell lymphopenia is seen in people with allergies and hypersensitivities, both of which are recognised components of well-defined ME/CFS as distinct from other syndromes of chronic fatigue.

It has long been acknowledged that a reduction in functional activity of suppressor T-cells and the loss of suppressor cell influence is implicated in the pathogenesis of autoimmune diseases (1,2,3,4) and evidence is now accumulating in the literature that ME/CFS is an autoimmune disease.

It has also been suggested that there may be an association between ME/CFS and mast cell activation disorder (5).

Evidence has certainly been presented for a causal involvement of pathologically active mast cells in interstitial cystitis, fibromyalgia and irritable bowel syndrome (6) and a link is suggested with POTS and dysautonomia (7), all of which are frequent co-morbidities with ME/CFS.

Mast cell activation disorder (MCAD) can cause tremendous suffering and disability: there is no cure for it and management is directed towards symptom control.

Mast Cell Activation Disorder

In the late 1980s the existence of mast cell activation disorders began to be discussed in the literature (8).

Mast cell activation disorder is formally categorised as an “orphan” disease, which means that many doctors know little about it and may not even be aware of it: lack of awareness by many medical professionals is currently a hurdle to proper diagnosis.

Mast cells are immune cells that release histamine and are involved not only in allergic diseases but also in inflammatory diseases (5). They are activated by IgE and

also by cytokines, environmental, food, infectious and drug triggers; they are profoundly activated by stress. They are found mostly in the skin and other connective tissues, but also in the lining of the lungs, stomach and intestines.

According to The Mastocytosis Society, mast cell disorders are caused by the proliferation and accumulation of genetically altered mast cells and/or the inappropriate release of mast cell mediators, creating symptoms in multiple organs, often without causing abnormalities in routine laboratory testing (6).

There are two main types of MCAD:

- (i) **Mast Cell Activation Syndrome (MCAS)**, which is non-proliferative: there are a normal number of mast cells but they over-react, so patients may experience most of the same symptoms as a person with mastocytosis but, importantly, they specifically lack urticaria pigmentosa; life span is normal
- (ii) **Mastocytosis**, in which there is proliferation of mast cells in multiple organs throughout the body; life span may be compromised.

Mastocytosis itself is categorised into **cutaneous** and **systemic** variants (9).

Urticaria pigmentosa (UP): this is the most common type of cutaneous mastocytosis (others types are diffuse cutaneous mastocytosis and mastocytoma of the skin). In UP, there are too many mast cells in the skin.

When it presents in adults, urticaria pigmentosa usually persists throughout life (9) and almost all such patients (97%) in fact have systemic mastocytosis (10); the risk of developing systemic mastocytosis increases with age. UP is characterised by many reddish-brown raised lesions on the skin of the trunk but not initially on the limbs. The lesions may be bumpy and are intensely itchy; at the outset, they may be mistaken for insect bites (11).

The presence of Darier's sign in urticaria pigmentosa is regarded as confirmation of systemic mastocytosis (10). Darier's sign is present when rubbing an affected lesion causes it and the surrounding skin to become visibly more red, itchy and swollen.

Bone marrow biopsy may be advised in patients with urticaria pigmentosa who also have abnormal blood and urine results, in particular, the level of tryptase in blood is elevated (> 15 ng/mL) and histamine levels in urine may be 2 to 3 times the normal level (N-methylhistamine/NMH and N-methylimidazole acetic acid are the two major metabolites of histamine found in the urine); metabolites of urinary prostaglandin D2 may also be found up to 150 times the normal level even when no symptoms of mastocytosis are present (12).

Systemic mastocytosis is characterised by the accumulation of mast cells in potentially every organ system but in particular, the gastrointestinal tract, the cardiovascular and the nervous systems: (synonym: systemic mast cell disease/SMCD); this can develop in the bones, heart, lungs, brain, spine, stomach and intestines. The clinical implications are substantial (10) and it is now classified by the WHO under myeloid neoplasms (13).

It can occur at any age but if it first appears in adults it is more serious: in about 30% of adult onset cases it is a risk factor for developing mast cell leukaemia, where abnormal collections of mast cells from connective tissue are present in the circulating blood.

Patients with systemic mastocytosis are advised to have an EpiPen always available and to avoid foods that are high in histamine and other substances, especially alcohol, that lead to the release of mast cell mediators.

Patients must also avoid certain medications, including salicylates (aspirin), opiates (including codeine), NSAIDs and thiamine (a vitamin) and any drugs containing quinine, as well as certain antibiotics, intravenous dextran and anaesthetics including muscle relaxants used during induction. They must also avoid contrast dyes used during radiographic examinations (5, 12).

Other known triggers include environmental toxins such as pesticides, especially perfumes and fragrances, food preservatives and colourings, monosodium glutamate and insect bites.

Systemic mastocytosis can cause the blood vessels to leak and become dilated; this can lead to circulatory collapse (14) and to a massive allergic reaction involving tachycardia, abdominal pain, explosive diarrhoea and sometimes anaphylaxis and loss of consciousness (15).

Other documented problems include flushing of the face, nasal congestion, vertigo, dizziness, swelling, wheezing, dyspnoea, sore throat, tingling tongue and lips, palpitations, chest pain, nausea, vomiting, bloating, oesophagitis (with difficulty in swallowing), mouth ulcers, excess gastric acid, malabsorption, steatorrhoea, headache, brain fog, ocular discomfort, muscle pain, bone pain, migratory arthritis, frequency of micturition and enlarged glands (especially the liver and spleen). Thrombocytopenia (a reduction in the number of platelets in the blood) may occur, resulting in slow coagulation. Fatigue and generalised malaise are prominent features.

Patients with MCAD should be kept under on-going medical review (typically seen twice a year) because of the unpredictable nature of the disorder (16).

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