

## **Brief Summary of Mast Cell Activation Disease (MCAD) and Mast Cell Activation Syndrome (MCAS)**

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*These notes are a follow-up to “Notes on Mast Cell Activation Disorder and ME/CFS” of 14<sup>th</sup> April 2017*

<http://www.margaretwilliams.me/2017/mast-cell-activation-disorder-and-mecfs.pdf> ).

The following notes on Mast Cell Activation Disease (MCAD) and specifically on Mast Cell Activation Syndrome (MCAS) come mostly from “Never Bet Against Occam: Mast Cell Activation Disease and the Modern Epidemics of Chronic Illness and Medical Complexity” by Lawrence B. Afrin MD (2016), to whom grateful acknowledgement is made. It is a 456-page manual that should be compulsory reading for all practising physicians of whatever speciality.

### **Background**

Mast Cell Activation Disease (or Disorder) is the generic term for two main categories: Mast Cell Activation Syndrome and systemic mastocytosis (SM); MCAS features inappropriate mast cell activation, with mediator production and release, whereas mastocytosis features mast cell proliferation where mast cells accumulate in potentially every organ system but in particular, the gastrointestinal tract, the cardiovascular and the nervous systems.

The widespread prevalence of mast cell disease is the opposite of what the medical profession has been teaching medical students: MCAS is more prevalent than mastocytosis and whilst mastocytosis is indeed rare, research suggests that 14 -19% of the general population is affected by MCAS.

Mast cell disease carries an increased risk of malignancy, especially lymphoma and leukaemia: mastocytosis is classified by the WHO under myeloid neoplasms and life span may be compromised.

Medical education on MCAS is woefully lacking: it is known as an “orphan” disease, which means that many doctors may not even be aware of it and the vast majority of physicians have no training in how to manage it.

Afrin refers to it as “*this lonely area of biomedical science*”; he states that 99% of the medical profession still think mast cell disease is only the rare cancer-like disease of too many mast cells (mastocytosis) that is impossible to treat, so to ameliorate this lack of professional awareness of MCAS, Afrin also aims to inform patients themselves about what is a very serious and increasingly prevalent disease that causes severe and usually life-long suffering.

### **The modern epidemic of chronic inflammatory diseases**

Afrin observes that the modern epidemics of chronic inflammatory diseases are increasingly being found to manifest inappropriate mast cell activation and he describes mast cell disease as “*a multi-headed Hydra*”: given how it has the potential to impact every system in the body and given its common clinical presentation with multi-system inflammation, Afrin queries whether MCAS is the root cause of branch disorders such as dysautonomia, irritable bowel syndrome, fibromyalgia; interstitial cystitis, lupus, mixed connective tissue disease, multiple sclerosis, multiple chemical sensitivity, POTS and Sjogren’s disease, amongst others, and it has also been suggested that there may be an association between ME/CFS and mast cell activation disorder (1), all of which have overlapping features.

Mast cells were first associated with disease in 1887 (this being the proliferative cutaneous mast cell disease urticaria pigmentosa seen in mastocytosis) and in the late 1980s the existence of mast cell activation disorders began to be discussed in the literature (2).

### A real disease

Afrin is unambiguous: copious data prove that MCAS is a real disease; different patterns of mast cell mutations lead to different patterns of aberrant release of a large spectrum of mast cell mediators; this in turn leads to a large spectrum of clinical presentation.

What is not yet known is whether it is a primary disease of mutational origin or a secondary disease reacting to some as yet unknown provocation. The most important research question is whether the mast cell is a normal mast cell reacting normally to provocation, or the result of an abnormal (ie. mutated) mast cell reacting abnormally to provocation, and/or whether the mast cell is reacting abnormally to no provocation at all.

Afrin states that MCAS is the ultimate chameleon and -- in stark contrast to psychiatrists such as Professor Sir Simon Wessely, known for his belief that some illnesses (including ME/CFS) can be treated without knowledge of the cause (3) – Afrin is clear: “*You can’t sensibly treat what you haven’t accurately diagnosed, so improving diagnosis is paramount*” and he gently chides the medical profession: “*You’ll never find it if you don’t look for it*”.

Most routine screening comes back as NAD (nothing abnormal discovered), so patients continue to be dismissed as suffering from MUS (medically unexplained symptoms), which carries the undeserved stigma of time-waster or malingerer, or are given an incorrect psychosomatic label because that is the easiest (and cheapest) option. Despite the mounting evidence that ME/CFS is an autoimmune disease (and despite its possible association with mast cell disease), adherents of the “Wessely School” retain their intransigent belief that ME/CFS is “*emotionally driven*” (4).

### Chronic polymorbidity mean difficulty in diagnosis

In MCAS there are chronic symptoms in multiple systems which cannot be explained by routine testing (ie. multi-system presentation with polymorbidity: no system in the body is immune to MCAS).

How can a physician recognise a disease that can present with virtually any complaint and which requires esoteric laboratory testing for confirmation of the diagnosis?

Major issues include inflammation, infection, autoimmunity, malignancy, coagulopathy and osteopathy; pain is body-wide.

Core MCAS symptoms include fatigue, rashes, itching and aching, together with associated constitutional symptoms, the full range of problems being unique to each individual patient. Afrin observes that: *“The range of issues (is) such that only MCAS could be the root issue”*.

It is well-established that mast cell disease can result in astonishingly severe and acute floods of aberrant mediator release and Afrin meticulously documents the protean symptomatology of MCAS system by system (see Appendix I below).

A major challenge facing MCAS patients is that many *“feel awful in general”* but externally appear *“OK”* even though they have felt so awful in so many different ways for such a long time: most newly diagnosed MCAS patients have been ill from the disease for decades.

Afrin knows from years of clinical experience that an incorrect diagnosis of psychosomatic illness is a huge problem (and the biggest problem) for MCAS patients, with ignorant and disbelieving physicians expressing their pseudo-wonder at *“how sick somebody can get just from thinking they’re sick”*.

Afrin states that the MCAS patient often faces great difficulty gaining initial control over the disease and even though for all practical purposes, mast cell disease cannot be cured, the MCAS patient’s doctor must keep in mind how differently the disease behaves in different patients.

Afrin comments that he has seen more than 1,000 patients with MCAS and has never seen patients so happy to be told there is a real illness explaining their years or decades of suffering: *“I guess it shouldn’t be surprising that when you’ve been sick in a myriad ways for a very long time and you’ve seen countless doctors (and received) countless diagnoses that don’t well account for your full range of troubles, it’s a relief to finally learn that there really is a biomedical abnormality – a disease – that can account for what’s been going on”*.

### Mutations

Research by Dr Gerhard J Molderings of the University of Bonn, an internationally acclaimed clinical immunologist whose expertise in MCAD is without question, has found that mutations are commonly present in the mast cell regulatory elements of MCAS patients and that such mutations are the principal drivers of the aberrant mast cell activation.

Many mutations have been found in the genes and proteins that regulate mast cell behaviour and many of these mutations result in mast cell misbehaviour: these mutationally-driven misbehaviours result in increases in processes that lead to the production and release of mediators.

MCAS can present clinically in so many different ways because different sets of mutations lead the cell to misbehave in different ways – in other words, different aberrant patterns of mediator production and release lead to very different patterns of clinical presentation.

Most of the known mast cell mutations result in the mast cell being *“always on”*.

The fundamental question is how so many different sets of mutations could develop (as repeatedly shown by Dr Gerhard Molderings at Bonn), which Afrin sees as the reality of MCAS.

### Mast cell mediators

Mast cells are known as the master regulators of the immune system: they produce and release very potent biochemical mediators including histamine (an important mediator of inflammation which causes itching and swelling) and cytokines, which interact with other cells and tissues.

Dysfunctional mast cells seen in MCAS can result in a wide array of aberrations in the immune system itself, including the production of autoantibodies.

TNF (tumour necrosis factor, a pro-inflammatory cytokine) is a well-established mast cell mediator and there is published evidence that it is raised in (ME)CFS:

*“We found that exercise induced a sustained elevation in the concentration of TNF- $\alpha$  which was still present three days later, and this only occurred in the CFS patients....The pro-inflammatory cytokine TNF- $\alpha$  is known to be a cause of acute sickness behaviour, characterised by reduced activity related to ‘weakness, malaise, listlessness and inability to concentrate’, symptoms also notable in CFS.... more intense exercise may induce pro-inflammatory cytokine release (TNF- $\alpha$ ) in patients with CFS” (5).*

There is a whole class of inflammatory mediators – interleukins – that are also produced and released by mast cells.

There are in fact more than 200 mediators that the mast cell is presently known to produce, only a few of which can be tested for: testing is very difficult to do because the mediators disappear within minutes if the specimen is not kept chilled, not only in transit but also by technicians in the laboratory, so there is great likelihood of the specimen being degraded and hence of a false negative result.

### Mast cell disease *can* be diagnosed

The most studied mast cell gene (and corresponding protein) is KIT, a transmembrane protein (ie. it is partly outside the cell membrane but with the majority inside the cell). The part that sticks outside the cell is called CD117 and this can be detected, as can CD25 (detectable by flow cytometry), this being the component of the receptor signalling protein interleukin-2 which is usually found on the surface of T-cells and never normally on the surface of the normal mast cell. Such specific staining (ie. CD117 and CD25) is a reliable marker for the presence of abnormal mast cells.

Afrin points out that: *“The biology of the mast cell virtually guarantees multi-system complexity, but we don’t need to accept that the disease is undiagnosable”* because most MCAS patients bear mutations in key regulatory elements in their mast cells and there is the additional possibility that autoantibodies directed against various elements of the mast cell surface might trigger activation, so although some of these diseases might manifest as the

autoimmune urticarias, it might well be possible for such autoimmune disorders to manifest non-urticarial forms of mast cell activation, therefore it is worthwhile checking for autoantibodies against the IgE receptor.

### The therapeutic goal

Regarding treatment, Afrin notes that the “*therapeutic goal*” does not mean feeling perfect or even significantly better all the time: the average MCAS patient should not expect ever again to feel perfectly healthy or never to deteriorate.

### The MCAS patient faces unlimited challenges

MCAS patients face constant difficulties: any change in an MCAS patient’s exposures has the potential to provoke adverse effects.

It is clear that in MCAS patients, their dysfunctional mast cells react to many environmental provocations in hyperactive fashion.

Visiting new places means exposure to multiple new foods and chemicals; some MCAS patients have significant dietary intolerances and are highly reactive to a wide assortment of foods; some have nutrient absorption problems, so pancreatic enzyme supplements may be helpful in MCAS patients whose symptom complexes include chronic pancreatitis and micronutrient malabsorption syndromes.

MCAS patients often respond intolerantly to therapies targeted at their ailments.

No medication consists solely of the active ingredient and any allegedly inactive ingredient (a filler, a binder or a dye in oral medication or a carrier fluid in intravenous medication) has the potential for triggering a flare of MCAS and such inactive ingredients are known to be toxic to MCAS patients.

Drugs such as NSAIDs (including aspirin) can trigger flares of mast cell activation to the point of anaphylaxis even at trivial doses.

New clothes may be pre-treated with some textile chemical which might provoke a mast cell reaction in MCAS patients.

### An Inheritability Factor?

It is known that the risk of MCAS in relatives of an MCAS patient is triple the risk in the general population.

Afrin comments that the severity of MCAS often moves up to a higher level following severe stress such as a road traffic accident, but that careful history-taking virtually always reveals symptoms of MCAS to have been present dating back to adolescence.

He deems it possible that there is some inheritable “genetic fragility factor” and that the disease becomes worse after exposure not only to a stressor such as a road traffic accident

but also after the patient is exposed to an infection, and that the stressor causes additional (non-inheritable) mutations.

He queries what this “genetic fragility factor” might be. Might it be a mutated epigene? (Epigenes are patterns of additional methyl groups to the DNA strands composing genes; an epigene controls how functional a gene is within a cell). Epigenetic mutations might predispose a given gene to become mutated if exposed to a stressor, or the genetic fragility factor might take the form of a hidden virus.

This remains hypothetical, but Afrin concludes that the variable interactions of inheritable fragility factors with variable stressors to variable mutations provide the best explanation for what has been observed clinically in MCAS patients.

### Conclusion

Afrin is aware that many MCAS patients have been so ill for so long that they have come to accept the illness as a baseline state: they know it would be pointless to mention their problems to any doctor as they have no reason to believe that any doctor would help them.

Afrin’s book is intended to change fundamentally such a distressing state of medical ignorance about MCAS and physicians’ consequent mismanagement of patients; both Afrin and his book deserve the highest accolades.

The MCAS community owes Afrin immeasurable gratitude.

No-one who reads his book can fail to understand both the prevalence and the devastating nature of mast cell disease.

### References:

1. Spectrum of mast cell activation disorders. Al Petra et al. Expert Review of Clinical Immunology 2014 (May): 10(6):729-739
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4. <http://www.virology.ws/2017/09/11/trial-by-error-the-nice-topic-expert-reports/>
5. Immunological changes after both exercise and activity in chronic fatigue syndrome: a pilot study. White PD, KE Nye, AJ Pinching et al. JCFS 2004:12 (2):51-66).

## APPENDIX I

### Symptomatology in Mast Cell Activation Syndrome

Afrin addresses the abnormalities and symptomatology of MCAS system by system: integumentary; immunological; gastrointestinal; cardiovascular; pulmonary; haematological and coagulatory; endocrinological and metabolic; musculoskeletal; lymphatic; ocular/ophthalmological; otological; oral/pharyngeal; genito-urinary and neuropsychiatric.

MCAS causes multi-system inflammation and general “*unwellness*” of an inflammatory nature: patients invariably have an extraordinarily complicated lifelong history of being unwell, with an uncountable number of medical evaluations that are consistently non-diagnostic.

There is undoubtedly an increased risk of malignancy, especially of haematological, bone marrow and gastro-intestinal malignancies.

Afrin records that the symptoms are “*everywhere*”; those documented by him are listed below, but in no particular or systemic order.

Fatigue and malaise can be variable but also substantial, unrelenting and utterly disabling -- these are among the most common symptoms in MCAS, as is diffuse pain, which is the dominant musculoskeletal issue and there is a clear decrease in muscle strength (legs suddenly “*give out*”). MCAS patients are often unable to stand up unsupported for any length of time.

Of interest is that random skin biopsies of fibromyalgia patients (whose primary problem is widespread pain) show approximately ten-fold more mast cells than healthy people.

Chronic “*all-over*” pain is common in MCAS; it may be intense, deep and burning; it is often migratory; there is invariably abdominal pain but also waxing/waning abdominal discomfort; Afrin notes that pain in the LUQ (left upper quadrant of the abdomen) is common and that it may be due to periodic aberrant release of inflammatory mediators by dysfunctional splenic mast cell leading to chronic splenomegaly; lymph glands may be tender and enlarged; there may be chronic idiopathic pancreatitis and malabsorption is common; there is often deep pelvic discomfort.

There is waxing/waning diffuse migratory pain in both large and small joints that is often crippling (for example, in the shoulders/elbows/knees); there may be on-going back pain; gout may be present; (or pseudogout, where the crystal deposits in the joint are calcium pyrophosphate dihydrate instead of sodium urate); headaches are frequent.

Episodic “*grabbing*” central chest pain is common: Afrin considers that it may be due to a flare of inflammation, or to spasm of the chest wall, oesophagus, lung or other thoracic structures; it may be so severe that it mimics a heart attack: indeed, it can affect blood vessels and cause a heart attack. Afrin says that MCAS: “*can drive the development of substantial vascular aberrations, both arterial and venous (eg. haemorrhoids)*”. Tachycardia and palpitations are common.

Chronic dyspnoea (shortness of breath) on minimal exertion is very common in MCAS.

Many MCAS patients exhibit haematological abnormalities and these can be virtually any haematological abnormality, for example there may be too many red cells or too few red cells; there may be too many white blood cells or too few white blood cells; there may be too many or too few platelets; there may be too much clotting or too little clotting leading to excessive and prolonged bleeding. There is slow wound healing and easy bruising.

There may be bilateral oedema in the lower extremities: it may be mistaken for a classic symptom of heart failure but, unlike in cardiac failure, the oedema is migratory – an MCAS patient may have intermittent pronounced oedema in both feet and ankles for months at a time and be unable to wear normal shoes, but then it disappears, only to occur in random places at random times, for example in the hands and fingers (so a ring cannot be worn) and in the face.

There is an increasing literature suggesting that mast cell disease can drive acute and chronic kidney disease and even kidney fibrosis (scarring).

Urinary issues are frequently seen in MCAS, including incontinence; polyuria (with excessive night-time urination) is characteristic of MCAS; interstitial cystitis (IC) is common: it is a mast-cell-driven disease caused by a flare-up of mast cell activation.

Diarrhoea is a notable feature in MCAS; it may be watery and occur 15 – 20 times daily; it may alternate with constipation; it is often accompanied by abdominal cramps and bloating; nausea may be chronic and severe; there may be chronic vomiting.

There may be dysphagia (difficulty swallowing, with a choking sensation) and mouth ulcers are common, as is gastro-oesophageal reflux (GERD).

There are both cellular and humoral immune defects in MCAS leading to immune dysfunction; patients have many allergies including food allergies, especially to dairy products; they exhibit odd and prolific sensitivities, including to heat, cold, UV radiation and exertion; there are also antigenic sensitivities, in particular to perfumes/ fragrances and also to coffee. They have adverse reactions to alcohol and to spicy foods, as well as to horsefly and other insect bites. They have a wide variety of medication sensitivities (including to excipients such as fillers, binders, preservatives, dyes and colouring agents).

There are problems with anaesthesia: anaesthetic agents are well-recognised provocateurs of mast cell disease.

Episodic migratory rashes are particularly common in MCAS: they are intensely itchy (urticaria); there may be frequent acute onslaughts of hives or the rash may resemble cutaneous lupus; if there is systemic mastocytosis, there may be urticaria pigmentosa.

MCAS patients have trouble with their skin (for example, bleeding from open skin lesions); with their nails (which show longitudinal ridges); with their teeth and with their hair: alopecia is common. Dermatographism is axiomatic. Fungal skin infections in the groin are common, as are “crawling” sensations on the skin.

MCAS patients may display episodic and mildly painful subcutaneous nodules which are distributed all over the body (particularly on the plantar surface of the feet).



Problems with eyesight are common in MCAS: there is chronic episodic visual blurring, sometimes with diplopia; there is irritation of the eyes; there is episodic unprovoked loss of visual focus and blepharospasm may be present.

A patient with MCAS suffers from unprovoked flushing, for example, of the face (often unilateral), ears and hands (this is not the same as hot flushes). Unprovoked flushing is virtually pathognomonic of MCAS.

There are temperature anomalies: an MCAS patient often feels cold all the time but unprovoked sweats are common; there may be fevers or chills.

Dysautonomia is frequently found in MCAS, with light-headedness; dizziness; frank vertigo; weakness and widely fluctuating blood pressure; problems with balance are common, resulting in falls; there is poor tolerance of positional changes.

Tremor is commonly seen in MCAS, as is tingling and numbness in fingers and toes; tinnitus is not uncommon; dysacusis (alterations in hearing) and hyperacusis all occur in MCAS.

Other common features of MCAS include a dry nose, with nasal congestion/stuffiness and unprovoked epistaxis; there may be episodic coughing; there is sleep dysregulation and bad nightmares occur in MCAS.

Low levels of vitamin B and vitamin D are a known problem in MCAS and there may be disruption of normal bone metabolism, with osteoporosis or osteosclerosis.

Neuropsychiatric symptoms in MCAS include cognitive dysfunction; emotional lability; panic attacks; anxiety and depression.