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Review

Postural orthostatic tachycardia syndrome and the potential role of mast cell activation

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ABSTRACT

Though a sizeable amount of data connects mast cell activity to the neurologic system, less is known about the true clinical implications of this relationship. Even less is understood about treatment strategies in those with both allergic and neurologic complaints. This is particularly true in postural orthostatic tachycardia syndrome (POTS), a common type of dysautonomia, where patients are burdened by symptoms of orthostatic cerebral hypoperfusion and several other comorbidities that are likely influenced by autonomic tone. Some patients describe characteristic allergic symptoms, in the absence of typical IgE mediated triggers, and also improvement with traditional mast cell directed medications. Further work is necessary to determine whether these anecdotal observations are valid. The answer to this question will likely be addressed as the mechanisms of POTS are better characterized, which may include a phenotype with distinct mast cell involvement.

1. Introduction

Postural orthostatic tachycardia syndrome (POTS) is a syndrome specific to excessive orthostatic tachycardia associated with a wide array of symptoms that often include orthostatic presyncope, palpitations, chest discomfort, dyspnea, and "brain fog" (Raj, 2013). These symptoms, as well as the postural tachycardia, are thought to result from cerebral hypoperfusion. Although specific findings on tilt table testing define POTS (> 30 beats per minute increase in heart rate from supine to upright posture), it is known that POTS is also frequently associated with a variety of other disorders including chronic abdominal pain, migraine headache, chronic fatigue, hypermobility and musculoskeletal pain (Rea et al., 2017; Garland et al., 2015).

In recent years, many neurologists and cardiologists specializing in POTS have anecdotally observed that the use of antihistamines and other mast cell directed therapies offers benefit to manage symptoms in some patients. Furthermore, a subset of patients often describes "allergic-like" reactions to a variety of stimuli including food, odors and medications. Thus, the allergist is increasingly requested to evaluate such patients. Complicating things further, POTS has been described secondary to a variety of mechanisms. Further study will be necessary to determine whether MCAS might be more likely in a specific subtype of POTS. This review focuses in part, on mast cell/nerve connectivity, but to what extent neuropathic components play a role in POTS are less clear. Scant literature exists in the realm of controlled medical studies to guide the management of such patients with POTS and allergic phenomena. Despite the paucity of literature, there is a larger body of evidence that mechanistically might link POTS to mast cell activation and is worth further discussion.

2. Mast cell activation syndrome in distinction to mastocytosis

The World Health Organization (WHO) criteria for systemic mastocytosis require either one major and one minor criterion or 3 minor criteria. The major criterion is multifocal dense infiltrates of mast cells (≥15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s). The minor criteria are a. > 25% of all mast cells are atypical cells on bone marrow smears or are spindle-shaped in mast cell infiltrates, b. *KIT* point mutation at codon 816 in the bone marrow or another extracutaneous organ, c. Mast cells in bone marrow or another extracutaneous organ with CD2 and/or CD25 expression, and d. Baseline serum tryptase > 20 ng/ml. In 2016, the World Health Organization classification of mastocytosis was updated to *include indolent systemic mastocytosis, smoldering systemic mastocytosis*, *systemic mastocytosis with an associated hematologic* (*non-mast cell lineage*) *neoplasm, aggressive systemic mastocytosis and mast cell leukemia* (Valent et al., 2017). Alternatively, it has been recognized that clonal mast cell disorders can be identified which do not meet WHO criteria for mastocytosis but have clonal markers of CD25+ mast cells in bone marrow or the KIT D816V mutation. These patients are diagnosed with *monoclonal mast cell activation syndrome* (Akin, 2017). In general, mastocytosis is relatively easy to exclude via serum tryptase and if any lingering question remains, with a bone marrow biopsy.

As opposed to mastocytosis, *mast cell activation syndrome* (MCAS) is

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characteristically defined by the combination of 1) typical symptoms, 2) laboratory abnormalities and 3) response to treatment. Symptoms should be concurrent with what would be expected related to mast cell mediator release. Symptomatic episodes should be associated with an elevation in validated mast cell markers and there should be some degree of improvement with targeted mast cell therapy (Molderings et al., 2011; Hamilton et al., 2011). The difficulties and pitfalls of the various laboratory studies are reviewed elsewhere (Akin, 2017). These three factors form a working diagnosis for MCAS and can be applied to patients with recurrent flushing, anaphylaxis, recurrent crampy abdominal pain, diarrhea, and itching. Many of these symptoms are present in patients with POTS and thus it is sensible to look for the presence of these diagnostic criteria.

In 2005, Shibao et al. evaluated 177 POTS patients. Their definition of MCAS included typical POTS criteria in addition to an elevated urine methylhistamine level during flushing episodes (Shibao et al., 2005). Eight females met criteria for POTS and MCAS, five patients presented with orthostatic hypotension and MCAS, and 16 individuals had POTS and flushing but no increase in urine methylhistamine. A final group of 12 healthy controls were included. Symptoms during an attack included flushing, palpitations lightheadedness, severe orthostatic intolerance, nausea, diarrhea, abdominal cramping and polyuria. In the group of patients with elevated methylhistamine, both histamine receptor 1 (H_1) and histamine receptor 2 (H_2) receptor antagonists were beneficial. These groups also had elevated norepinephrine levels demonstrating a hyperadrenergic phenotype. Methyldopa or methyldopa in combination with antihistamines was also found to be helpful. The authors noted hypertensive episodes that could be misinterpreted as a pheochromocytoma. This report nicely ties in the role of histamine in a minority of POTS patients. This clinical observation is supported by Li et al. who used double-labeled immunofluorescence to demonstrate co-localization of histamine and noradrenalin in sympathetic nerves suggesting that histamine might function as a neurotransmitter in modulation of sympathetic function (Li et al., 2006).

3. Bidirectional aspects of mast cell and nerve activity – mast cell effects on nerves

There is a large body of literature concerning the interdependency of mast cells and neuronal function. In fact, many of the traditional symptoms associated with allergic reactions such as itchy eyes, bronchospasm, and mucous production are mediated to a large degree by neuronal activity (Undem & Taylor-Clark, 2014). Anatomically, mast cells are frequently found in close approximation to nerve endings and thus any mediator release from the mast cell might have specific effects on nerve function (Arizono et al., 1990; Schemann & Camilleri, 2013). Afferent C fibers express both transient receptor family members TRPV1 and TRPA1, either of which can be activated by several mast cell mediators including histamine 1 agonists, bradykinin 2 receptor agonists, and lipid mediators such as prostaglandin D_2 metabolites (Shim et al., 2007; Suh & Oh, 2005; Taylor-Clark et al., 2008a). C-fibers also express receptors for leukotrienes ($CysLT_1$), tryptase and others thus potentially conveying local mast cell mediator release in a widespread fashion via neurologic transmission. Although specific activation of the neuron might occur via mast cell mediator release, another mechanism might be the alteration in the excitability of the nerve. In trigeminal nerves, LTD_4 acting at $CysLT_1$ does not singularly activate the nerve, but makes the trigeminal nerve much more susceptible to activation through other stimuli (Taylor-Clark et al., 2008b).

Mast cells can affect neuronal activity – tryptase directly activates proteinase-activated receptors expressed on neurons (Corvera et al., 1999). Cysteinyl leukotrienes and prostaglandins influence the local nerve environment (Marone et al., 2002) with tumor necrosis factor α and nerve growth factor causing changes in local nerves to lower threshold activation (van Houwelingen et al., 2002; Leon et al., 1994). Thus, there are a multitude of mast cell mediators that can acutely modulate nerve function in complex and novel ways.

Furthermore, it is clear that after allergic stimulation, nerves can undergo phenotypic changes. These changes might be responsible for longer-term effects that may persist after the resolution of typical mast cell mediators (Pan et al., 2010). Neurotrophin release is widely observed after allergic stimulation (Bonini et al., 1999). Nerve growth factor (NGF) binds to tyrosine kinase receptor A (TrkA) on nerve terminal membranes triggering internalization of the NGF-TrkA complex. This complex travels to the cell body thus influencing neuronal gene transcription. Interestingly, inhibition of cysteinyl leukotrienes binding to $CysLT_1R$ with montelukast (currently used as an allergy and MCAS neurogenesis treatment) in animal models reduced neuroinflammation, promoted and restored blood brain barrier function suggesting long term changes in nerve structure and function after interaction with mast cell products (Huber et al., 2011; Marschallinger et al., 2015). In an animal model of repeated allergen inhalation challenge, a shift from vasoactive intestinal peptide/nitric oxide neurons to cholinergic type is observed – a shift which alters the balance of airway tone from relaxation to contraction (Pan et al., 2010).

4. Bidirectional aspects of mast cell and nerve activity – nerve effects on mast cell

Mast cells can form membrane-membrane contact with nerve cells in vivo (Stead et al., 1987; Stead et al., 1989). Nerves contain substance P and CGRP, both of which can act on mast cells through their own specific receptors (Stead et al., 1987; Keller & Marfurt, 1991). Thus nerve stimulation can lead to mast cell activation. Recent work clarifies the physical connection of mast cell and nerve. SgIGSF/SynCAM is localized preferentially on both sides of most synapses in the brain and functions as a hemophilic adhesion molecule that spans the synaptic cleft (Biederer et al., 2002). Under the control of microphthalmia transcription factor (MITF), SgIGSF expression occurs in bone marrow derived mast cells (Ito et al., 2003). Synaptic differentiation could be induced in these non-neuronal cells at the contact site with neuronal cells when non neuronal cells were transfected with SgIGSF/SynCAM and glutamate receptor cDNAs (Biederer et al., 2002).

Furuno et al. then further investigated the connection of mast cells and neurons (Furuno et al., 2005). They showed that cultured superior cervical ganglion (SCG) neurites expressed SgIGSF along their entire length. SgIGSF co-localized intensively at the contact site between mast cells and SCG neuritis, whereas SgIGSF deficient mast cells did not bind well (Furuno et al., 2005). The mast cell growth factor receptor c- KIT was not physically part of the connection, yet c-KIT was necessary for SgIGSF to function normally as an adhesion molecule (Koma et al., 2005) in mast cells attached to fibroblasts. The authors concluded that SgIGSF does not simply serve as glue in nerve-mast cell interaction, but also to promote the development of a microenvironment in which mast cells have an enhanced susceptibility to nerve activation (Furuno et al., 2005).

5. Autoimmune activation of mast cells

Mast cells may participate in autoimmunity either through mediator production or as effector cells stimulated by autoantibodies. Patients with chronic urticaria often have IgG antibodies to the high affinity IgE receptor Fc epsilon R1 (FcεR1) that can induce mast cell activation (Kolkhir et al., 2017). Recently, cohorts of patients with POTS are found to have adrenergic or muscarinic autoantibodies. (Li et al., 2014; Fedorowski et al., 2017) Mast cells express several adrenergic and muscarinic receptors and, thus, it is conceivable that these autoantibodies could modulate mast cell function directly.

Though there are no studies showing that autoantibodies found in POTS serum can activate mast cells, there is evidence that adrenergic and muscarinic receptors are active in regulation of mast cell function. Autoantibodies directed against both the alpha-1 adrenoreceptor and

the angiotensin II AT-1 receptor activated rat cardiac mast cells. (Okruhlicova et al., 2007) Further, β2 adrenergic receptors are generally thought to reduce mast cell degranulation and thus the β2 agonistic antibodies found in POTS may at first appear to potentially lower mast cell responses. (Kay & Peachell, 2005) However, there is also data to suggest that the initial mast cell inhibition by pharmacologic β2 agonists may actually lead to a reduction in β2 receptor expression and over time resulting in a hyperresponsive state of the cells. (Kay & Peachell, 2005) (White et al., 2018). Additionally, mast cell cytokine production of IL-6, IL-8, and IL-13 by IL-1 was enhanced by NE and blocked by propranolol but not by β1selective antagonists (Chi et al., 2004) suggesting that there may be differential and complex responses of mast cells to β2 modulation. The idea that beta-blocker therapy in POTS may exacerbate MCAS or allergic features is not well founded given the safety of cardioselective beta-blockers in many patients with asthma and allergic disease and trials should not be avoided because of this theoretical risk. (Morales et al., 2017) In patients with severe POTS and MCAS, the theoretical risk of using a non-selective beta blocker such as propranolol should be considered. This issue, as well as the decision to use injectable epinephrine in a beta-blocked patient is complex and warrants an extensive discussion between the patient, the allergist and the cardiologist or neurologist. (Lieberman & Simons, 2015). Although, the concern in this situation is that epinephrine would be less effective, it still should be given if medically necessary. A recent analysis of anaphylaxis in the emergency room, did not find an increase need for a second dose of injectable epinephrine in beta blocked patients.

Alpha-1 adrenergic receptor autoantibodies detected in POTS serum have agonistic activity at the receptor but also prevent phenylephrine-induced contraction of vessels compared to controls suggesting concomitant antagonistic activity. Mast cells express alpha-1 adrenergic receptors and in murine mast cells, phenylephrine or norepinephrine increased histamine release though other studies have suggested a protective effect of NE (Grisanti et al., 2011). Importantly, one study clearly demonstrated that agonistic autoantibodies to alpha-1 and angiotensin 2 (AT1) receptors isolated from patients with hypertension that were cultured with rat heart mast cells increased both mast cell maturation and degranulation (Okruhlicova et al., 2007). At 3 days after culture, mast cells treated with autoantibodies were larger and more granulated, whereas at 10 days the cells were degranulated compared with control treated cells. These reports suggest that autoantibodies in vitro are capable of influencing multiple aspects of mast cell responses.

Agonistic β1 autoantibodies are of particular interest in POTS, due to activation of cardiac chronotropic events and have been shown to correlate with upright HR (Fedorowski et al., 2017) β1 receptors are expressed on mast cells though their function is unclear (Chi et al., 2004). The complexity of potential in-vivo adrenergic autoantibody responses is critical to keep in mind as they also act as partial agonists or modulators at their respective receptors (Li et al., 2014; Fedorowski et al., 2017) Thus, initial ligation may lead to partial activation, but bound autoantibody may lead to allosteric changes that function overall as antagonists. Therefore, mast cell activation or inhibition may occur depending on an individual patient's repertoire and local presence of such autoantibodies. In addition to adrenergic antibodies, cholinergic pathways (muscarinic and nicotinic) also modulate mast cells (Nazarov & Pronina, 2012; Tokura, 2016) and anti-muscarinic antibodies have been detected in some POTS patients suggesting that these antibodies may also be active in mast cell responses (Okruhlicova et al., 2007; Dubey et al., 2016). Taken together, mast cells can clearly be activated by autoantibodies as is the case with autoimmune chronic urticaria and further work is needed to determine whether autoantibodies in POTS can also contribute to mast cell responses.

6. Mastocytosis and autonomic function

One can look at this entire relationship from the other perspective. If mast cell dysfunction has a causative role in the pathophysiology of POTS it could be expected that mastocytosis would be strongly associated with POTS. Although this does not appear to have ever been formally studied, some studies have evaluated the neurologic aspects of mastocytosis.

Neurotrophins, a group of nerve growth factors playing a critical role in the growth and maintenance of nerve fibers, have been shown to act on the maturation and survival of mast cells. (Groneberg et al., 2005; Groneberg et al., 2007) Peng et al. observed elevated expression of the neurotrophin receptors TrkA, TrkB and TrkC in human skin mast cells from mastocytosis subjects when compared with non-mastocytosis subjects. Peripheral CD117+ (CKIT) cells can migrate up a NGF-β gradient via TrkA on mast cells. (Peng et al., 2013) This demonstrates the significant role that neurotrophins might have in the pathology of systemic mastocytosis.

In a large survey of mastocytosis patients evaluating quality of life, the majority of mastocytosis/MCAS patients experienced lightheadedness (70.8%) daily or occasionally. (Jennings et al., 2014) Additionally 21.7% experienced daily extreme fatigue and 14.8% with daily severe abdominal pain. Other symptoms frequently experienced in this group of mastocytosis patients included brain fog or cognitive difficulties, diarrhea, headache, joint pain, bloating, anxiety and bone pain. This list overlaps considerably with frequent comorbidities seen in most POTS cohorts. Tryptase is a prototypical mast cell derived protein, which can be used after an allergic reaction to prove mast cell involvement or can be measured at baseline. When elevated at baseline, an expansion of the mast cell compartment likely exists and when elevated > 20 ng/mL, a workup for mastocytosis is generally indicated. It has been observed that many patients with an elevated tryptase do not have mastocytosis yet remain at risk for increased frequency and severity of allergy reaction as well as less specific symptoms of vertigo, muscle/bone pain, palpitations and diarrhea (Fellinger et al., 2014).

Mast cells produce and secrete a tremendous amount of mediators, many of which have hemodynamic effects and may be relevant to POTS. Although not exclusively produced by mast cells; histamine, prostaglandins, platelet activating factor, and adenosine all can be produced by mast cells and might have an important role in POTS related vasodilation and tachycardia (Parson et al., 2013; Romero et al., 2017; Vadas et al., 2008). Blocking these mediators could have an overall beneficial effect in POTS patients with MCAS and merits further study in POTS specifically.

7. Hypertryptasemia

In 2014, Lyons and colleagues published their findings related to the inheritance pattern of hypertryptasemia (Lyons et al., 2014). They initially described 9 index patients with familial analysis noting elevated tryptase in an autosomal dominant pattern. No patients had a clonal mast cell disorder. They found 26/33 subjects with episodic symptoms typical for mast cell activation including urticaria, flushing, abdominal pain, and diarrhea. 10 subjects had a history of anaphylaxis. Within this group of 33 individuals, 28 had either chronic or episodic gastrointestinal symptoms, 31 were atopic (mostly allergic rhinitis and asthma) and 23 had connective tissue abnormalities. Furthermore, 11/33 had chronic musculoskeletal pain, 10/33 had POTS and a neuropsychiatric diagnosis was present in 17/33 (Lyons et al., 2014). The authors noted that connective tissue abnormalities have been observed in mast cell disorders (Frischmeyer-Guerrerio et al., 2013).

In 2016, Lyons and colleagues expanded their report to include 96 patients from 35 families. (Lyons, 2016) In this study the genetic defects associated with familial hypertryptasemia were identified in germ-line duplications or triplications in the TPSAB1 gene encoding alpha-tryptase. The authors were able to replicate their initial associations with a

variety of functional disorders such as irritable bowel syndrome, chronic musculoskeletal pain, and diffuse arthralgia all seen at 3–5 fold higher prevalence than the general population. They again observed 46% with autonomic dysfunction as evidenced by an elevated COMPASS 31 score; 1/3 of this group had abnormal tilt table testing. Additional observations were systemic reactions to hymenoptera stings at 2-3× the frequency of the general population, and 39% with sleep disruption. The authors demonstrated a gene-dose effect where symptom severity and tryptase level worsened with increase in TPSAB1 copy number. The authors termed this condition *hereditary alpha-hypertryptasemia*, and in those individuals with significant symptoms suggested *hereditary alpha-tryptasemia syndrome* (Lyons, 2016). It is unclear by what mechanism the symptoms occur and what role, if any, the elevated tryptase value has in this disorder. Tryptase copy number is not clinically available, although a relatively simple surrogate would be obtaining serum tryptase in several first-degree relatives. If elevated in an autosomal dominant pattern, familial hypertryptasemia is likely. Based on the experience of the authors, an elevated tryptase level is uncommon in POTS.

8. Mast cell activation and hypermobility

Previous reports suggest that hypermobility connective tissue disorders such as Ehlers-Danlos type 3 (EDS3), hypermobility type, are associated with the presence of dysautonomia including POTS (Gazit et al., 2003; Kanjwal et al., 2010). Anecdotally, there has been the suggestion that POTS, MCAS, and hypermobile EDS may co-exist as a triad suggesting some common mechanisms (Cheung & Vadas, 2015). Clearly, the work of Lyons et al. shows that hereditary hypertryptasemia syndrome include connective tissue (CT) laxity, mast cell activation, and POTS and is thus supportive of the co-existence of these disorders (Lyons, 2016). Recently, patients with connective tissue abnormalities including those with EDS have been found to have increased risk of developing eosinophilic esophagitis (Abonia et al., 2013). Mast cells are thought to be critically involved in eosinophilic esophagitis and perhaps dysregulation of the CT-mast cell axis is an important contributor to the disease. As mast cells are found in high numbers in connective tissue surrounding blood vessels and throughout the body, bidirectional communication with the extracellular matrix (ECM) in CT may be important for both mast cell responses and CT homeostasis. Interestingly, ECM stretch alone induces mast cell degranulation (Fowlkes et al., 2013) and perhaps CT laxity as is found in hypermobile EDS, might promote mast cell activation via persistent exaggerated CT stretch in such patients. Mast cells possess a stretch-sensitive chloride channel that may underlie activation after stretch, as is also relevant to conditions such as dermatographism (Wang et al., 2010). Mast cell proteases can also induce abnormal remodeling of the ECM that might in turn might lead to reciprocal abnormal mast cell responses and drive a vicious cycle of attempts to repair abnormal CT resulting in persistent mast cell activation (da Silva et al., 2014). Other mechanistic possibilities linking MCAS and EDS include a predisposition to autoimmunity in EDS patients (Rodgers et al., 2017), that then secondarily promotes MCAS via autoantibodies or other immune activation of mast cells. Large-scale studies are currently being performed to better characterize the possible co-existence of POTS, EDS, and MCAS, which will likely be a springboard for future investigations into overlapping features and mechanisms of disease.

9. Treatment

Treatment for mast cell activation syndromes primarily focuses on blocking the effects of known mast cell mediators, namely histamine, leukotrienes and prostaglandin metabolites. Initiating treatment with H_1 receptor antagonists, H_2 receptor antagonists, and a $CysLT_1$ receptor antagonist are generally first line. The use of cromones is also frequently used early in the course of treatment. In the United States, cromolyn is available for oral, inhaled, intranasal, and ocular use. A similar compound, ketotifen, is available in the United States only in topical ocular formulation, yet is available in an oral form with systemic bioavailability in many other countries in the world.

Omalizumab is approved for treatment of chronic spontaneous urticaria and severe allergic asthma. It is a humanized monoclonal antibody directed at the Fc portion of the IgE molecule. Its effectiveness in chronic urticaria cannot be explained simply by depletion of serum IgE, therefore a modifying effect on mast cells or basophils is suspected. Given this, there have been limited case reports and case series which review successful experience of omalizumab treatment on symptoms in mastocytosis or idiopathic anaphylaxis (Bell & Jackson, 2012; Kibsgaard et al., 2014; Paraskevopoulos et al., 2013; Broesby-Olsen et al., 2018; Hughes et al., 2018). The authors are not aware of any published cases with omalizumab treatment of MCAS in a patient with POTS. Omalizumab can rarely cause anaphylaxis, but is otherwise felt to be safe and does not have an immunosuppressive role. It could be considered in a POTS patient with MCAS and significant cutaneous involvement.

10. Cromolyn sodium mechanism

Cromolyn specifically merits further attention. This particular medication has been available on the United States market since the 1970s. Although it clearly has a mast cell blocking effect, the mechanism of this effect has been elusive. Cromolyn disodium, through an unknown mechanism, inhibits mast cell activation and thereby diminishes the early and late phase allergic response to antigen challenge. (Holgate & Polosa, 2008)

More recently, several studies have shed light on new mechanisms for cromolyn action. In a survey of compounds with activation at GPR35, a G protein coupled receptor signaling through the G_i pathway, both mast cell stabilizers cromolyn and nedocromil had activity at the human GPR35 receptor (Yang et al., 2010) Zaprinast is a phosphodiesterase inhibitor with clinical mast cell stabilization effect. Neither cromolyn nor nedocromil have phosphodiesterase inhibitor activity yet all three compounds act at GPR35 and have similar mast cell stabilizing activity suggesting this effect could be specific to the GPR35 receptor. GPR35 is observed on mast cells, basophils, and eosinophils and is upregulated after mast cell exposure to IgE antibodies. (Yang et al., 2010) More pertinent to this article, GPR35 has been described to be a $G\alpha_{i/o}$ – coupled inhibitor of synaptic transmission. (Mackenzie & Milligan, 2017) Both kynurenic acid and zaprinast act as agonists at heterologous GPR35/CXCR8 in rat sympathetic neurons. Human GPR35/CXCR8 is highly expressed in human small intestine, colon and stomach. GPR35/CXCR8 is present and functional in rat dorsal root ganglia (Taniguchi et al., 2006; Ohshiro et al., 2008). In animal models, the GPR35/CXCR8 agonists kynurenic acid, zaprinast, and pamoic acid were able to have an anti-nociceptive effects (Cosi et al., 2011; Zhao et al., 2010).

Schemann and colleagues used the mast cell activation compound 48/80 to study neuronal specific effects (Schemann et al., 2012). Compound 48/80 is a well-known direct mast cell activator (does not require IgE specificity or cross-linking) and is used for this purpose in a plethora of studies evaluating mast cell pathways. Compound 48/80 has effects on pain, dorsal root ganglia and sympathetic neuron activation. A traditional paradigm had been that the primary effect was mast cell activation thereby affecting adjacent neurons. In this study, compound 48/80 directly activated enteric nerves and visceral afferents via a mast cell independent pathway (both on isolated dorsal root ganglia, nodose neurons and also in cultured myenteric neurons where mast cell were proven to be absent). Curiously, cromolyn attenuated the activity of compound 48/80 despite the fact that these experimental models were intentionally devoid of mast cells. Compound 48/80 has recently been found to signal mast cell activation through a novel pathway MGRPRX2 a recently identified G protein coupled receptor is

found to transduce the mast cell activation of a large variety of endogenous (substance P, VIP, antimicrobial host defense peptides) and exogenous factors (flouroquinolones, neuromuscular blockers, peptidergic drugs). This receptor may be important in mast cell directed neurogenic inflammation. (Subramanian et al., 2016)

A broad review of treatment approaches in mast cell activation syndromes is beyond the scope of this article and is reviewed elsewhere (Molderings et al., 2011; Afrin et al., 2016). In general, treatment is focused on blocking mast cell mediator activity with the intention of improving symptoms and quality of life. It should be noted that other than anecdotal observations, and the single study by Shibao et al. (2005), the authors are unaware of further data that treatment directed at mast cell mediators is specifically beneficial for POTS, although this has been widely observed clinically in a subset of POTS patients. This is an area where further study is necessary, but clinicians should be increasingly aware of the potential connection with mast cell/allergic symptoms and POTS.

11. Clinical application

It is understood that considerable variation exists in the assessment and treatment of comorbid mast cell activation in POTS. The following guidelines are suggested in the initial evaluation and treatment of such patients.

1. Testing for mast cell activation, specifically in the setting of POTS, has not been well validated. The highest yield for testing would likely be during an acute flare of symptoms strongly suspicious for mast cell activation (flushing, itching, coughing, nasal congestion, tachycardia).
2. The most common tests for mast cell activation are urinary studies for *N*-methyl histamine, 11-beta prostaglandin F2α, leukotriene E_4 and serum tryptase. Urinary testing can be done on 24 or 4-hour urine collection and should be kept chilled to optimize mediator identification.
3. Tryptase elevation is not always seen in anaphylaxis, but when seen is relatively specific for mast cell involvement.
4. Negative testing may not preclude mast cell involvement. The clinical experience of many POTS specialists suggests that empiric addition of safe mast cell medications may confer benefit in POTS patients.
5. The diagnosis of MCAS should be reserved for patients who meet the three major criteria: laboratory evidence of mast cell involvement, symptoms typical for mast cell activation and improvement with mast cell directed therapy.
6. It is unlikely that mast cell activation is a prominent component in all patients with POTS and thus empiric treatment with mast cell medications should not be continued indefinitely if no benefit is observed
7. The use of expensive, more targeted therapies should be reserved for those patients in which a firm diagnosis of mast cell activation exists
8. Given the reasonably low cost and relative safety, consideration should be made for a therapeutic trial with H_1 antagonists, H_2 antagonists, cromolyn, and montelukast in patients with POTS and symptoms consistent with MCAS.
9. Doses of up to fourfold daily dosing of the long acting non-sedating antihistamines may be more effective than single daily dosing for some patients
10. Suggested approach to treatment includes the addition of the above medications in sequential fashion. Each treatment should be assessed for effectiveness and if ineffective should be discontinued.
11. Even when MCAS is unequivocally present in a patient with POTS, it is unclear to what degree the POTS symptoms will respond to mast cell therapy.

POTS is a multifactorial syndrome with its own significant morbidity, frequently associated with other syndromes which might be equally disabling to the patient including abdominal pain, migraine, fatigue and repeated allergic type symptoms. The interconnectedness of mast cells and neuronal function offer a paradigm where the mast cell might be an effector arm of the autonomic system – or that inappropriate mast cell functioning drives neuronal dysregulation. Further, autoimmunity may also be a link between POTS and mast cell activation. A tremendous amount of research is needed to understand how common the MCAS phenotype is in POTS patients, what treatment modalities might be most effective, and whether mast cell activity has a primary role in the disorder or plays a secondary role to disordered autonomic control.

References

Abonia, J.P., Wen, T., Stucke, E.M., Grotjan, T., Griffith, M.S., Kemme, K.A., et al., 2013. High prevalence of eosinophilic esophagitis in patients with inherited connective tissue disorders. J. Allergy Clin. Immunol. 132 (2), 378–386.

Afrin, L.B., Butterfield, J.H., Raithel, M., Molderings, G.J., 2016. Often seen, rarely recognized: mast cell activation disease–a guide to diagnosis and therapeutic options. Ann. Med. 48 (3), 190–201.

Akin, C., 2017. Mast cell activation syndromes. J. Allergy Clin. Immunol. 140 (2), 349–355.

Arizono, N., Matsuda, S., Hattori, T., Kojima, Y., Maeda, T., Galli, S.J., 1990. Anatomical variation in mast cell nerve associations in the rat small intestine, heart, lung, and skin. Similarities of distances between neural processes and mast cells, eosinophils, or plasma cells in the jejunal lamina propria. Lab. Investig. 62 (5), 626–634.

Bell, M.C., Jackson, D.J., 2012. Prevention of anaphylaxis related to mast cell activation syndrome with omalizumab. Ann Allergy Asthma Immunol 108 (5), 383–384.

Biederer, T., Sara, Y., Mozhayeva, M., Atasoy, D., Liu, X., Kavalali, E.T., et al., 2002. SynCAM, a synaptic adhesion molecule that drives synapse assembly. Science 297 (5586), 1525–1531.

Bonini, S., Lambiase, A., Levi-Schaffer, F., Aloe, L., 1999. Nerve growth factor: an important molecule in allergic inflammation and tissue remodelling. Int. Arch. Allergy Immunol. 118 (2–4), 159–162.

Broesby-Olsen, S., Vestergaard, H., Mortz, C.G., Jensen, B., Havelund, T., Hermann, A.P., et al., 2018. Omalizumab prevents anaphylaxis and improves symptoms in systemic mastocytosis: efficacy and safety observations. Allergy 73 (1), 230–238.

Cheung, I., Vadas, P., 2015. A new disease cluster: mast cell activation syndrome, postural orthostatic tachycardia syndrome, and Ehlers Danlos Syndrome. J. Allergy Clin. Immunol. 135((2), AB65.

Chi, D.S., Fitzgerald, S.M., Pitts, S., Cantor, K., King, E., Lee, S.A., et al., 2004. MAPK-dependent regulation of IL-1- and beta-adrenoreceptor-induced inflammatory cytokine production from mast cells: implications for the stress response. BMC Immunol. 5, 22.

Corvera, C.U., Déry, O., McConalogue, K., Gamp, P., Thoma, M., Al-Ani, B., et al., 1999. Thrombin and mast cell tryptase regulate guinea-pig myenteric neurons through proteinase-activated receptors-1 and -2. J. Physiol. 517 (Pt 3), 741–756.

Cosi, C., Mannaioni, G., Cozzi, A., Carlà, V., Sili, M., Cavone, L., et al., 2011. G-protein coupled receptor 35 (GPR35) activation and inflammatory pain: studies on the antinociceptive effects of kynurenic acid and zaprinast. Neuropharmacology 60 (7–8), 1227–1231.

Dubey, D., Hopkins, S., Vernino, S., 2016. M1 and M2 muscarinic receptor antibodies among patients with postural orthostatic tachycardia syndrome: potential disease marker. J. Clin. Neuromuscul. Dis. 17 (3), 179.

Fedorowski, A., Li, H., Yu, X., Koelsch, K.A., Harris, V.M., Liles, C., et al., 2017. Antiadrenergic autoimmunity in postural tachycardia syndrome. Europace 19 (7), 1211–1219.

Fellinger, C., Hemmer, W., Wöhrl, S., Sesztak-Greinecker, G., Jarisch, R., Wantke, F., 2014. Clinical characteristics and risk profile of patients with elevated baseline serum tryptase. Allergol Immunopathol (Madr) 42 (6), 544–552.

Fowlkes, V., Wilson, C.G., Carver, W., Goldsmith, E.C., 2013. Mechanical loading promotes mast cell degranulation via RGD-integrin dependent pathways. J. Biomech. 46 (4), 788–795.

Frischmeyer-Guerrerio, P.A., Guerrerio, A.L., Oswald, G., Chichester, K., Myers, L., Halushka, M.K., et al., 2013. TGFβ receptor mutations impose a strong predisposition for human allergic disease. Sci. Transl. Med. 5 (195), 195ra94.

Furuno, T., Ito, A., Koma, Y., Watabe, K., Yokozaki, H., Bienenstock, J., et al., 2005. The spermatogenic Ig superfamily/synaptic cell adhesion molecule mast-cell adhesion molecule promotes interaction with nerves. J. Immunol. 174 (11), 6934–6942.

Garland, E.M., Celedonio, J.E., Raj, S.R., 2015. Postural tachycardia syndrome: beyond orthostatic intolerance. Curr Neurol Neurosci Rep. 15 (9), 60.

Gazit, Y., Nahir, A.M., Grahame, R., Jacob, G., 2003. Dysautonomia in the joint hypermobility syndrome. Am. J. Med. 115 (1), 33–40.

Grisanti, L.A., Perez, D.M., Porter, J.E., 2011. Modulation of immune cell function by α(1)-adrenergic receptor activation. Curr. Top. Membr. 67, 113–138.

Groneberg, D.A., Serowka, F., Peckenschneider, N., Artuc, M., Grützkau, A., Fischer, A., et al., 2005. Gene expression and regulation of nerve growth factor in atopic dermatitis mast cells and the human mast cell line-1. J. Neuroimmunol. 161 (1–2), 87–92.

Groneberg, D.A., Fischer, T.C., Peckenschneider, N., Noga, O., Dinh, Q.T., Welte, T., et al., 2007. Cell type-specific regulation of brain-derived neurotrophic factor in states of allergic inflammation. Clin. Exp. Allergy 37 (9), 1386–1391.
Hamilton, M.J., Hornick, J.L., Akin, C., Castells, M.C., Greenberger, N.J., 2011. Mast cell activation syndrome: a newly recognized disorder with systemic clinical manifestations. J. Allergy Clin. Immunol. 128 (1) (147–52.e2).
Holgate, S.T., Polosa, R., 2008. Treatment strategies for allergy and asthma. Nat. Rev. Immunol. 8 (3), 218–230.
van Houwelingen, A.H., Kool, M., de Jager, S.C., Redegeld, F.A., van Heuven-Nolsen, D., Kraneveld, A.D., et al., 2002. Mast cell-derived TNF-alpha primes sensory nerve endings in a pulmonary hypersensitivity reaction. J. Immunol. 168 (10), 5297–5302.
Huber, C., Marschallinger, J., Tempfer, H., Furtner, T., Couillard-Despres, S., Bauer, H.C., et al., 2011. Inhibition of leukotriene receptors boosts neural progenitor proliferation. Cell. Physiol. Biochem. 28 (5), 793–804.
Hughes, J.D.M., Olynyc, T., Chapdelaine, H., Segal, L., Miedzybrodzki, B., Ben-Shoshan, M., 2018. Effective management of severe cutaneous mastocytosis in young children with omalizumab (Xolair). Clin. Exp. Dermatol. 43 (5), 573–576.
Ito, A., Jippo, T., Wakayama, T., Morii, E., Koma, Y., Onda, H., et al., 2003. SgIGSF: a new mast-cell adhesion molecule used for attachment to fibroblasts and transcriptionally regulated by MITF. Blood 101 (7), 2601–2608.
Jennings, S., Russell, N., Jennings, B., Slee, V., Sterling, L., Castells, M., et al., 2014. The Mastocytosis Society survey on mast cell disorders: patient experiences and perceptions. J Allergy Clin Immunol Pract 2 (1), 70–76.
Kanjwal, K., Saeed, B., Karabin, B., Kanjwal, Y., Grubb, B.P., 2010. Comparative clinical profile of postural orthostatic tachycardia patients with and without joint hypermobility syndrome. Indian Pacing Electrophysiol J. 10 (4), 173–178.
Kay, L.J., Peachell, P.T., 2005. Mast cell beta2-adrenoceptors. Chem Immunol Allergy 87, 145–153.
Keller, J.T., Marfurt, C.F., 1991. Peptidergic and serotoninergic innervation of the rat dura mater. J. Comp. Neurol. 309 (4), 515–534.
Kibsgaard, L., Skjold, T., Deleuran, M., Vestergaard, C., 2014. Omalizumab induced remission of idiopathic anaphylaxis in a patient suffering from indolent systemic mastocytosis. Acta Derm. Venereol. 94 (3), 363–364.
Kolkhir, P., Church, M.K., Weller, K., Metz, M., Schmetzer, O., Maurer, M., 2017. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. J. Allergy Clin. Immunol. 139 (6) (1772–81.e1).
Koma, Y., Ito, A., Watabe, K., Hirata, T., Mizuki, M., Yokozaki, H., et al., 2005. Distinct role for c-kit receptor tyrosine kinase and SgIGSF adhesion molecule in attachment of mast cells to fibroblasts. Lab. Investig. 85 (3), 426–435.
Leon, A., Buriani, A., Dal Toso, R., Fabris, M., Romanello, S., Aloe, L., et al., 1994. Mast cells synthesize, store, and release nerve growth factor. Proc. Natl. Acad. Sci. U. S. A. 91 (9), 3739–3743.
Li, M., Hu, J., Chen, Z., Meng, J., Wang, H., Ma, X., et al., 2006. Evidence for histamine as a neurotransmitter in the cardiac sympathetic nervous system. Am. J. Physiol. Heart Circ. Physiol. 291 (1), H45–51.
Li, H., Yu, X., Liles, C., Khan, M., Vanderlinde-Wood, M., Galloway, A., et al., 2014. Autoimmune basis for postural tachycardia syndrome. J. Am. Heart Assoc. 3 (1), e000755.
Lieberman, P., Simons, F.E., 2015. Anaphylaxis and cardiovascular disease: therapeutic dilemmas. Clin. Exp. Allergy 45 (8), 1288–1295.
Lyons, J.J., Sun, G., Stone, K.D., Nelson, C., Wisch, L., O'Brien, M., et al., 2014. Mendelian inheritance of elevated serum tryptase associated with atopy and connective tissue abnormalities. J. Allergy Clin. Immunol. 133 (5), 1471–1474.
Lyons, J.J., Yu, X., Hughes, J.D., Le, Q.T., Jamil, A., Bai, Y., et al., 2016. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. Nat. Genet. 48 (12), 1564–1569.
Mackenzie, A.E., Milligan, G., 2017. The emerging pharmacology and function of GPR35 in the nervous system. Neuropharmacology 113 (Pt B), 661–671.
Marone, G., Galli, S.J., Kitamura, Y., 2002. Probing the roles of mast cells and basophils in natural and acquired immunity, physiology and disease. Trends Immunol. 23 (9), 425–427.
Marschallinger, J., Schäffner, I., Klein, B., Gelfert, R., Rivera, F.J., Illes, S., et al., 2015. Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. Nat. Commun. 6, 8466.
Molderings, G.J., Brettner, S., Homann, J., Afrin, L.B., 2011. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. J. Hematol. Oncol. 4, 10.
Morales, D.R., Lipworth, B.J., Donnan, P.T., Jackson, C., Guthrie, B., 2017. Respiratory effect of beta-blockers in people with asthma and cardiovascular disease: population-based nested case control study. BMC Med. 15 (1), 18.
Nazarov, P.G., Pronina, A.P., 2012. The influence of cholinergic agents on histamine release from HMC-1 human mast cell line stimulated with IgG, C-reactive protein and compound 48/80. Life Sci. 91 (21 − 22), 1053–1057.
Ohshiro, H., Tonai-Kachi, H., Ichikawa, K., 2008. GPR35 is a functional receptor in rat dorsal root ganglion neurons. Biochem. Biophys. Res. Commun. 365 (2), 344–348.
Okruhlicova, L., Morwinski, R., Schulze, W., Bartel, S., Weismann, P., Tribulova, N., et al., 2007. Autoantibodies against G-protein-coupled receptors modulate heart mast cells. Cell. Mol. Immunol. 4 (2), 127–133.
Pan, J., Rhode, H.K., Undem, B.J., Myers, A.C., 2010. Neurotransmitters in airway parasympathetic neurons altered by neurotrophin-3 and repeated allergen challenge. Am. J. Respir. Cell Mol. Biol. 43 (4), 452–457.
Paraskevopoulos, G., Sifnaios, E., Christodoulopoulos, K., Mantopoulou, F., Papakonstantis, M., Sabaziotis, D., 2013. Successful treatment of mastocytic anaphylactic episodes with reduction of skin mast cells after anti-IgE therapy. Eur Ann Allergy Clin Immunol 45 (2), 52–55.
Parson, H.K., Harati, H., Cooper, D., Vinik, A.I., 2013. Role of prostaglandin D2 and the autonomic nervous system in niacin-induced flushing. J Diabetes 5 (1), 59–67.
Peng, W.M., Maintz, L., Allam, J.P., Raap, U., Gütgemann, I., Kirfel, J., et al., 2013. Increased circulating levels of neurotrophins and elevated expression of their high-affinity receptors on skin and gut mast cells in mastocytosis. Blood 122 (10), 1779–1788.
Raj, S.R., 2013. Postural tachycardia syndrome (POTS). Circulation 127 (23), 2336–2342.
Rea, N.A., Campbell, C.L., Cortez, M.M., 2017. Quantitative assessment of autonomic symptom burden in postural tachycardia syndrome (POTS). J. Neurol. Sci. 377, 35–41.
Rodgers, K.R., Gui, J., Dinulos, M.B., Chou, R.C., 2017. Ehlers-Danlos syndrome hypermobility type is associated with rheumatic diseases. Sci. Rep. 7, 39636.
Romero, S.A., McCord, J.L., Ely, M.R., Sieck, D.C., Buck, T.M., Luttrell, M.J., et al., 2017. Mast cell degranulation and de novo histamine formation contribute to sustained postexercise vasodilation in humans. J Appl Physiol (1985) 122 (3), 603–610.
Schemann, M., Camilleri, M., 2013. Functions and imaging of mast cell and neural axis of the gut. Gastroenterology 144 (4), 698–704.e4.
Schemann, M., Kugler, E.M., Buhner, S., Eastwood, C., Donovan, J., Jiang, W., et al., 2012. The mast cell degranulator compound 48/80 directly activates neurons. PLoS One 7 (12), e52104.
Shibao, C., Arzubiaga, C., Roberts, L.J., Raj, S., Black, B., Harris, P., et al., 2005. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. Hypertension 45 (3), 385–390.
Shim, W.S., Tak, M.H., Lee, M.H., Kim, M., Koo, J.Y., Lee, C.H., et al., 2007. TRPV1 mediates histamine-induced itching via the activation of phospholipase A2 and 12-lipoxygenase. J. Neurosci. 27 (9), 2331–2337.
da Silva, E.Z., Jamur, M.C., Oliver, C., 2014. Mast cell function: a new vision of an old cell. J. Histochem. Cytochem. 62 (10), 698–738.
Stead, R.H., Tomioka, M., Quinonez, G., Simon, G.T., Felten, S.Y., Bienenstock, J., 1987. Intestinal mucosal mast cells in normal and nematode-infected rat intestines are in intimate contact with peptidergic nerves. Proc. Natl. Acad. Sci. U. S. A. 84 (9), 2975–2979.
Stead, R.H., Dixon, M.F., Bramwell, N.H., Riddell, R.H., Bienenstock, J., 1989. Mast cells are closely apposed to nerves in the human gastrointestinal mucosa. Gastroenterology 97 (3), 575–585.
Subramanian, H., Gupta, K., Ali, H., 2016. Roles of mas-related G protein-coupled receptor X2 on mast cell-mediated host defense, pseudoallergic drug reactions, and chronic inflammatory diseases. J. Allergy Clin. Immunol. 138 (3), 700–710.
Suh, Y.G., Oh, U., 2005. Activation and activators of TRPV1 and their pharmaceutical implication. Curr. Pharm. Des. 11 (21), 2687–2698.
Taniguchi, Y., Tonai-Kachi, H., Shinjo, K., 2006. Zaprinast, a well-known cyclic guanosine monophosphate-specific phosphodiesterase inhibitor, is an agonist for GPR35. FEBS Lett. 580 (21), 5003–5008.
Taylor-Clark, T.E., Undem, B.J., Macglashan, D.W., Ghatta, S., Carr, M.J., McAlexander, M.A., 2008a. Prostaglandin-induced activation of nociceptive neurons via direct interaction with transient receptor potential A1 (TRPA1). Mol. Pharmacol. 73 (2), 274–281.
Taylor-Clark, T.E., Nassenstein, C., Undem, B.J., 2008b. Leukotriene D4 increases the excitability of capsaicin-sensitive nasal sensory nerves to electrical and chemical stimuli. Br. J. Pharmacol. 154 (6), 1359–1368.
Tokura, Y., 2016. New etiology of cholinergic Urticaria. Curr. Probl. Dermatol. 51, 94–100.
Undem, B.J., Taylor-Clark, T., 2014. Mechanisms underlying the neuronal-based symptoms of allergy. J. Allergy Clin. Immunol. 133 (6), 1521–1534.
Vadas, P., Gold, M., Perelman, B., Liss, G.M., Lack, G., Blyth, T., et al., 2008. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. N. Engl. J. Med. 358 (1), 28–35.
Valent, P., Akin, C., Metcalfe, D.D., 2017. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood 129 (11), 1420–1427.
Wang, L., Ding, G., Gu, Q., Schwarz, W., 2010. Single-channel properties of a stretch-sensitive chloride channel in the human mast cell line HMC-1. Eur. Biophys. J. 39 (5), 757–767.
White, J., Greger, K., Sangil, L., Kahoud, R., Li, J., Lohse, C., et al., 2018. Patients taking Beta-blockers do not require increased doses of epinephrine for anaphylaxis. Journal of Allergy and Clinical Immunology: In Practice (In Press).
Yang, Y., Lu, J.Y., Wu, X., Summer, S., Whoriskey, J., Saris, C., et al., 2010. G-protein-coupled receptor 35 is a target of the asthma drugs cromolyn disodium and nedocromil sodium. Pharmacology 86 (1), 1–5.
Zhao, P., Sharir, H., Kapur, A., Cowan, A., Geller, E.B., Adler, M.W., et al., 2010. Targeting of the orphan receptor GPR35 by pamoic acid: a potent activator of extracellular signal-regulated kinase and β-arrestin2 with antinociceptive activity. Mol. Pharmacol. 78 (4), 560–568.