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DISCUSSION

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# Mast cell activation may explain many cases of chemical intolerance

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## Abstract

**Background:** This paper explores the relationship between chemical intolerance (CI) and mast cell activation syndrome (MCAS). Worldwide observations provide evidence for a two-stage disease process called toxicant-induced loss of tolerance (TILT) as a mechanism for CI. TILT is initiated by a major exposure event or a series of lower-level exposures. Subsequently, affected individuals report that common chemical inhalants, foods, and drugs (i.e., various xenobiotics) trigger multi-system symptoms.

**Purpose:** To determine whether MCAS provides a plausible biological mechanism for CI/TILT.

**Methods:** Using the validated Quick Environmental Exposure and Sensitivity Inventory (QEESI), we compared patients diagnosed with MCAS ($n = 147$) to individuals who reported chemical intolerances (CI/TILT) following various exposures ($n = 345$) and to healthy controls ($n = 76$). Using ANOVA, we compared QEESI scores across groups. Clinical scores for the MCAS patient group were used to predict CI status using logistic regression.

**Results:** More than half (59%) of the MCAS group met criteria for CI. A logistic regression model illustrates that as the likelihood of patients having MCAS increased, their likelihood of having CI/TILT similarly increased, to a near-perfect correspondence at the high ends of the QEESI and clinical MCAS scores. Symptom and intolerance patterns were nearly identical for the CI and MCAS groups.

**Discussion:** We present data suggesting that xenobiotic activation of mast cells may underlie CI/TILT. The strikingly similar symptom and intolerance patterns for MCAS and TILT suggest that xenobiotics disrupt mast cells, leading to either or both of these challenging conditions. Faced with patients suffering from complex illness affecting multiple organ systems and fluctuating inflammatory, allergic, and dystrophic symptoms, clinicians can now ask themselves two questions: (1) Could MCAS be at the root of these problems? (2) Could environmental exposures be driving MC activation and mediator release? Increasing our understanding of the connection between TILT and MCs has the potential to expose a new link between environmental exposures and illness, offering new opportunities for improving individual and public health.

**Conclusion:** The close correspondence between QEESI scores and symptom patterns for MCAS and TILT patients supports xenobiotic-driven mast cell activation and mediator release (i.e., MCAS) as a plausible unifying biological mechanism for CI/TILT, with profound implications for medicine, public health, and regulatory toxicology.

**Keywords:** Chemical intolerance, Drug intolerance, Environmental exposure, Food intolerance, Mast cell, Mast cell activation syndrome, Regulatory toxicology, Toxicant-induced loss of tolerance (TILT), Xenobiotics, Allergies

## Introduction

### Chemical intolerance

Chemical, food, and drug intolerances are growing international concerns [1–5]. These intolerances may arise following exposures to building construction or

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remodeling, pesticides, military environments (e.g., Gulf War), combustion products (e.g., World Trade Center disaster, burn pits, wildfires), chemical spills or releases, surgical implants, mold, and many other sources [6, 7]. The exposures may be a one-time acute event; a series of exposures; or long-term, low-level exposures. They often involve particular synthetic chemicals such as an organophosphate pesticide, a combination of synthetic substances, and/or their combustion products. These xenobiotics enter the body via well-known routes: inhalation, ingestion, skin contact, and/or injection/implantation. What remains unclear is why a subset of individuals would subsequently develop multi-system symptoms and persistent intolerances to chemicals, and often foods and drugs, which never bothered them before and do not bother most people. Over the past 70 years, strikingly similar reports have emerged from patients, doctors, and researchers around the world supporting chemical intolerance (CI) as a novel, or at least previously unrecognized, disease.

Many patients attribute onset of their illness and intolerances to a well-defined exposure event [7, 8]. (Readers are directed to this study's companion paper addressing CI initiating events [7]). Different family members or coworkers who become ill frequently exhibit different manifestations, confounding physicians and investigators [6]. Individuals affected by a *particular* infectious agent or toxicant often share recognizable constellations of symptoms. This is not the case for CI patients, which has hampered efforts to establish a consensus case definition for CI. It also suggests a mechanism for CI which is distinct from other infectious/toxicant exposures.

There is accumulating evidence for a two-stage causal model linking xenobiotic exposures to subsequent intolerances first described by Miller in 1996 as toxicant-induced loss of tolerance (TILT) [9]. The origins of these intolerances variously have been attributed to classical toxicity, allergy, and psychological factors [10–12]. Up to now, an understandable biological mechanism for them has remained elusive.

#### Mast cells

In the last decade, our understanding of the evolutionarily ancient mast cell (MC) and its ability to effect a host of inflammatory, allergic, and other responses throughout the body has expanded rapidly [13–15]. Several factors have resulted in a likely underestimation of the MC's pivotal role in disease: (1) since the discovery of IgE, allergy's principal focus has been on the humoral, as opposed to the cellular, immune system; (2) MCs' typically tiny numbers and their sparse distribution in most tissues have contributed to their anonymity; and (3) MCs are minimally present in the blood, and even where they are present, it has been a challenge to identify and isolate them [16–20].

These sentinel cells guard the perimeters of our skin and other organs, warding off invaders and protecting our internal milieu. They serve as first responders to most bodily invasions and insults. Mast cells originate in the bone marrow and migrate to the interface between our tissues and the external environment [14, 15]. They are highly evolved, critical components of the cellular immune system [15], supporting both innate and adaptive immunity. Largely lying in wait, these warriors spring into action if they perceive a major threat, releasing a vast array of mediators all at once.

Once triggered, MCs can deploy more than 1000 distinct cell-surface mediator receptors [21] resulting in inflammation, allergic-like phenomena, or altered tissue growth and development (dystrophism) [22, 23]. See Additional file 1: Table S1 for representative examples of key mast cell mediators. MCs respond to a wide variety of antigenic triggers and physical forces, causing release of pre-stored and/or newly synthesized mediators particular to the insult and its anatomic location [8, 16, 17]. Appropriate MC mediator release helps tissues resist and recover from insults; aberrant release is harmful in ways specific to the locations and patterns of the released mediators. Preliminary investigations suggest highly heterogeneous, complex profiles of somatic MC regulatory gene mutations drive many cases of MCAS [24].

We have long been aware of MCs' ability to precipitate anaphylaxis in response to bee stings, peanuts, and other allergens in previously sensitized individuals. MC's release of histamine into the surrounding tissues and bloodstream leads to immediately recognizable hives, hypotension, syncope, respiratory arrest, and even death [25, 26]. We now understand, however, that there is an extensive array of other mediators that MCs selectively release in response to varying stimuli, including low molecular weight chemicals like formaldehyde and volatile organic compounds [21, 27]. The MC's enormous repertoire of cell-surface receptors can identify an extraordinary array of signals and effect precise responses [15, 17, 21]. Even while a MC is launching its pre-formed armaments, it signals other cells to join the battle. Meanwhile, behind the frontline, MCs are reloading their weapons and stockpiling new munitions [22, 23, 25, 26]. Thus, our so-called "primitive" immune system is, in fact, quite sophisticated. It was many decades following the discovery of IgE and its relationship to anaphylaxis and classical allergies (such as pollen, animal dander, and dust mites) that we learned of MCs' capacity to respond to a vast range of stimuli—revealing new, alternative pathways for their activation and

degranulation, even in the absence of "classic" binding of antigen with immunoglobulins.

The fact that CI individuals often report immediate symptoms following seemingly insignificant exposures, such as a whiff of fragrance, has led some to speculate that the mechanism underlying CI must be neurological. However, MCs can explosively release, or gradually leak, their mediators. In fact, there is no cellular element of the immune system that reacts faster than mast cells. Lymphocytes take hours to activate, neutrophils require minutes, but MCs can respond to a trigger in sub-second time [16, 17, 28].

A crucial link between our contemporary exposures and our ancient MCs appears to have been missed. The MC's evolutionary path stretches back to half a billion years [13, 15]. In contrast, emergence of the chemical industry, associated with the industrial revolution, took place only a few hundred years ago (1760–1820). Since WWII, more and more synthetic organic chemicals have crept into our personal environments. In response to the oil embargo and energy conservation efforts in the 1970s, many homes and buildings were sealed more tightly, resulting in insufficient fresh air to dilute contaminants. This has resulted in the accumulation of every sort of indoor air pollutant to levels higher than ever before (e.g., volatile, and semi-volatile organic chemicals outgassing from new construction and remodeling materials, pesticides, mold, disinfectants, and cleaning agents) [6, 7]. Only now are we learning that our contemporary exposures may be provoking MCs to release their inflammatory mediators, resulting in a condition often referred to as "mast cell activation syndrome" (MCAS) [29].

Although proposed diagnostic criteria for MCAS [29, 30] differ in some respects, MCAS diagnosis typically requires: (1) chronic and/or recurrent symptoms consistent with aberrant MC mediator release; (2) exclusion of other conditions which might better explain the patient's symptoms; and (3) laboratory evidence of MC activation (i.e., MC mediator release). Most MCAS patients respond to MC-targeted treatments, thus providing an important diagnostic clue [31].

By one estimate, 10–17% of the German population may have MCAS [32]. CI prevalence estimates range from 8 to 33% in population-based surveys [33–35]. Hojo et al. [2] in Japan and Steinemann [1] in the U.S. each conducted surveys of chemical intolerance in their respective countries on two separate occasions, a decade apart. According to their research, in just 10 years, substantial increases in CI occurred in both countries.

We propose mast cell mediator release, initiated and triggered by xenobiotics, as a plausible biological mechanism underlying many, if not most, cases of CI and TILT. If MCAS and CI are closely related, they should share similar pathophysiologies and exhibit parallel symptoms and intolerances. In this paper, we explore converging lines of evidence supporting MCAS as a plausible unifying explanation for CI/TILT.

## Methods

The MCAS group consisted of patients of authors LBA and TTD who were seen between September 2017 and April 2018. Patients were assigned a clinical score reflecting their likelihood of having MCAS using a validated MCAS assessment instrument [36, 37]. Patients also completed the Quick Environmental Exposure and Sensitivity Inventory (QEESI) along with their intake forms [31, 38]. The QEESI is a validated 50-item questionnaire, which is considered the international reference standard for assessing CI (see Palmer et al., for a list of 72 peer-reviewed journal articles using the QEESI in 16 countries with a total of over 32,000 respondents [39]). The QEESI has four scales: Symptom Severity, Chemical Intolerances, Other Intolerances, and Life Impact. Each scale item is scored from 0 to 10 (0 = "not a problem" to 10 = "severe or disabling problem"). Total scale scores range from 0 to 100. There is also a 10-item Masking Index which gauges ongoing exposures (such as to caffeine, tobacco, or drugs) that can reduce, or mask, individuals' awareness of their intolerances [40]. Responses to the Chemical Exposure Scale explicitly ask participants to respond to how a specific chemical exposure makes them feel. The Symptom Severity Scale asks about common symptoms the person is having, not necessarily associated with the specific exposures on the Chemical Intolerance Scale.

QEESI scores from MCAS patients were compared to QEESI scores derived from earlier published data involving five different groups: CI individuals who identified an initiating exposure event; CI individuals who reported no initiating exposure; implant recipients; Gulf War Veterans; and a control group [38]. Those with QEESI scores of 40 or greater on both the Symptom Severity and Chemical Intolerance Scales were classified as having CI in our predictive model. Mean scores were compared statistically using ANOVA across groups using Tukey post hoc tests.

Clinical scores for the MCAS patient group were used to predict CI status using a logistic regression model. Analyses were performed using SAS software [41]. This study was approved by the University of Texas Health Science Center at San Antonio Internal Review Board (approval number HSC20150821H).

## Results

### Percentage meeting CI criteria by group

There were 147 patients from the MCAS clinic, ranging in age from 16 to 75 years (mean = 40.7, SD = 13.9). The exposure and control comparison groups were derived from published data by Miller and Prihoda [38]. The number, percent female, age, and percentages meeting CI criteria are presented in Table 1 for all six groups. Fifty-nine percent (59%) of the MCAS clinical group met QEESI criteria for CI, a somewhat higher percentage than among the Gulf War Veterans (49%). Percentages of the other comparison groups meeting CI criteria exceeded 75%, except for controls (7%).

### QEESI total scale scores

Figure 1 shows the distribution of total QEESI scores and masking indices by participants in these groups. In every case, controls' scores were significantly lower than for the other groups ($p < 0.001$). With few exceptions, the CI groups scored significantly higher than other groups, whether or not they reported an initiating exposure. Regarding the *Chemical Intolerance* Scale, scores for the MCAS group were not significantly different from the Gulf War Veterans' scores, but were significantly lower than scores of all other groups. On the *Other Intolerance* Scale, the MCAS group scored significantly higher than the Gulf War Veterans' group ($p < 0.01$); however, the MCAS group's scores were statistically equivalent to the other groups' scores. On the Life Impact Scale, the MCAS group's score did not differ significantly from the implant group's, and both were significantly higher than the Gulf War Veterans group ($p < 0.01$). For the Symptom Severity Scale, the Implant group and the CI with known exposure group scored significantly higher than the other groups ($p < 0.01$). Scores for the CI group without a preceding exposure and the MCAS groups did not differ significantly from each other. The Masking Index (a measure of ongoing exposures) was significantly greater among controls compared to the other groups ($p < 0.01$), except for the Gulf War Veterans whose Masking Index score was not significantly different from that of controls. The MCAS group and the CI group with known exposures had similarly low masking scores.

**Table 1** Percentages meeting TILT/CI criteria by group

| Group | n | % female | Age Mean (± se) | % meeting criteria for TILT/CI[c] |
|---|---|---|---|---|
| CI-exposure event [a] | 96 | 49% | 49 (11) | 89% |
| CI-no event [a] | 90 | 82% | 51 (12) | 81% |
| Implant [a] | 87 | 50% | 50 ( 9) | 75% |
| MCAS group [b] | 147 | 89% | 41 (14) | 59% |
| Gulf Veterans [a] | 72 | 11% | 40 (10) | 49% |
| Controls [a] | 76 | 68% | 43 ( 9) | 7% |

[a] From Miller and Prihoda [38]

[b] MCAS clinical group (Sept 2017 to April 2018)

[c] Scores ≥ 40 on both the QEESI Chemical Exposures and Symptom Severity Scales qualify as CI

### Predicted probability of CI with increases in MCAS scores

Logistic regression results appear in Table 2. Compared to the lowest quartile (Q1), those in the 2nd quartile of MCAS scores were 2.6 times more likely to have CI ($p = 0.027$). Those in the 3rd quartile of MCAS scores were 6.0 times more likely to have CI ($p = 0.0001$); those in the 4th quartile of MCAS scores were 6.2 times more likely to have CI ($p = 0.0001$).

Figure 2 shows that the probability of CI increases as MCAS scores increase. There is an exponential increase in the probability of CI with increasing MCAS scores, reaching near-perfect prediction toward the extreme set of MCAS scores.

### Distribution of QEESI scores

Figures 3, 4, 5, 6 and 7 show QEESI scale items for TILT, MCAS, and Control groups. Here we merged four groups into one group (TILT group) for purposes of comparison against controls and MCAS patients: CI individuals who reported an initiating exposure (pesticides, remodeling); Gulf War Veterans; implant patients; and the CI individuals who did not report an initiating exposure event but had qualifying QEESI scores.

#### *Symptom Severity Scale (Fig. 3)*

There were no significant differences between the TILT and MCAS groups for 8 of the 10 symptom items. For the neuromuscular and affective items, the TILT group's scores were slightly higher than those of the MCAS group ($p < 0.04$). Both the TILT and MCAS groups reported significantly more severe symptoms than did controls ($p < 0.0001$).

#### *Chemical Intolerance Scale (Fig. 4)*

TILT and MCAS groups both had significantly higher chemical intolerance scores than did controls ($p < 0.0001$). The TILT group's chemical intolerance scores were significantly higher than the MCAS group's scores for all items ($p < 0.01$).

#### *Other Intolerance Scale (Fig. 5)*

There were no significant differences between the TILT and MCAS groups for 8 of the 10 other intolerance items. Only the chlorinated tap water item was scored significantly higher by the TILT group ($p < 0.01$). Only the foods/food-additives item was scored significantly

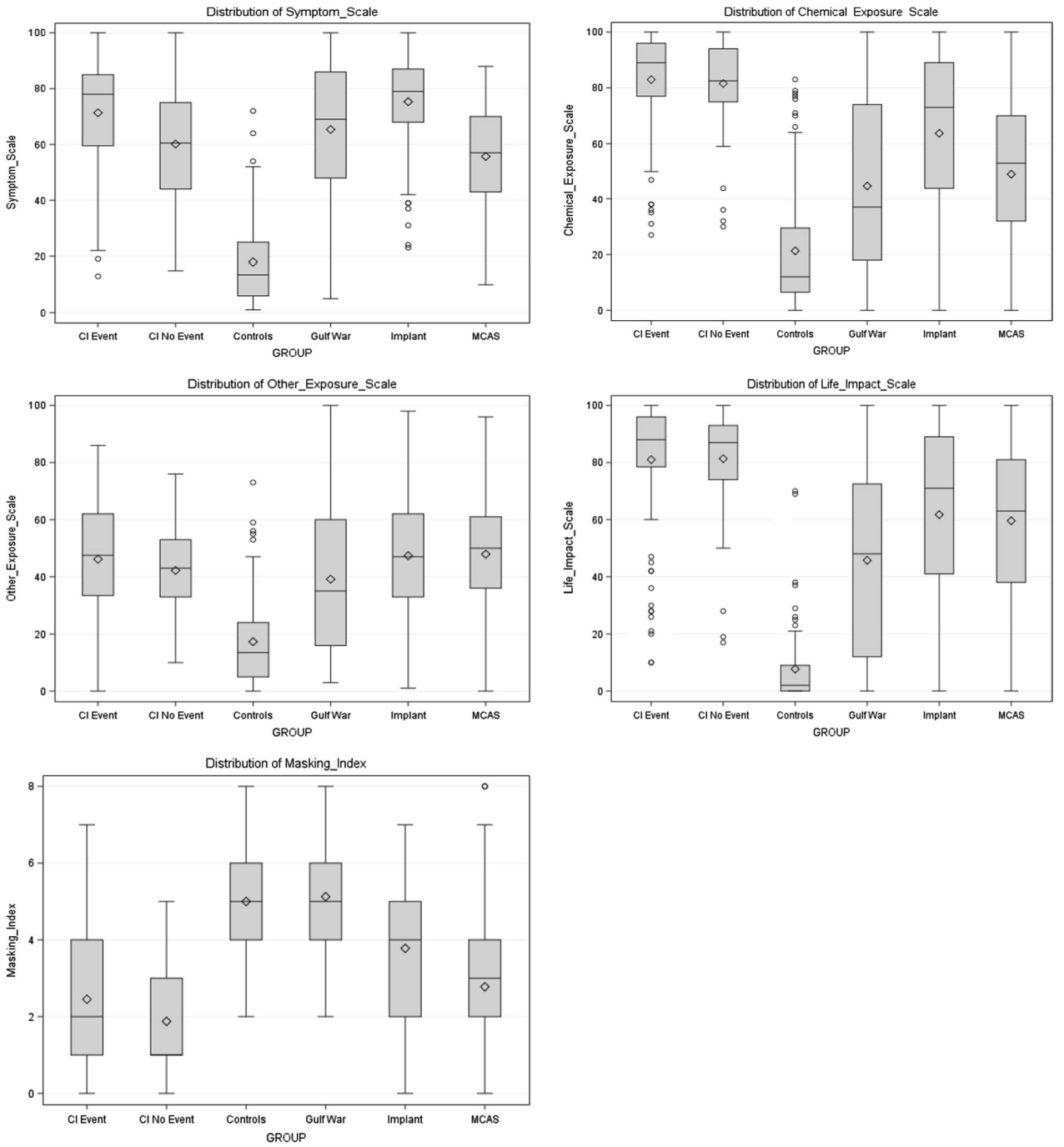


**Fig. 1** QEESI total scale scores by group

higher by the MCAS group ($p < 0.03$). Both TILT and MCAS groups scored significantly higher than controls ($p < 0.0001$).

***Life Impact Scale (Fig. 6)***

Both TILT and MCAS groups scored significantly higher than controls ($p < 0.0001$) on all Life Impact items. The

**Table 2** Logistic regression model predicting TILT status from MCAS quartile scores

| Quartile comparison | Parameter estimate (± se) | p value | Odds ratios (95% confidence limits) |
|---|---|---|---|
| *Unadjusted maximum likelihood estimates* | | | |
| Q2 v Q1 | 0.96 (0.44) | 0.0265 | 2.62 (1.12–6.16) |
| Q3 v Q1 | 1.79 (0.60) | 0.0001 | 6.00 (2.43–14.80) |
| Q4 v Q1 | 1.83 (0.47) | 0.0001 | 6.22 (2.45–15.79) |
| *Maximum likelihood estimates adjusted for age and gender* | | | |
| Q2 v Q1 | 0.96 (0.44) | 0.0300 | 2.60 (1.09–6.19) |
| Q3 v Q1 | 1.69 (0.47) | 0.0003 | 5.45 (2.18–13.62) |
| Q4 v Q1 | 1.79 (0.48) | 0.0002 | 5.98 (2.33–15.33) |

TILT group consistently scored higher on 9 of the 10 items on this scale than did the MCAS group ($p < 0.01$), with the exception of the diet item where the MCAS group reported a slightly greater impact of their illness on diet.

#### *Masking Index (Fig. 7)*

Both TILT and MCAS groups had significantly lower masking scores than did controls ($p < 0.0001$), meaning that they had fewer ongoing exposures to tobacco smoke, fragrances, caffeine, or certain drugs which tend to hide ("mask") the relationship between symptoms and exposures. The MCAS group reported greater use of drugs/medications and gas stoves than did the TILT group ($p < 0.05$).

## Discussion

For decades, both MCAS and CI patients have been misunderstood, marginalized, and often referred for mental health evaluation [6, 42, 43], with practitioners assigning diagnostic labels such as Somatic Symptom Disorder, Multiple Chemical Sensitivity (MCS), or Idiopathic Environmental Intolerances (IEI). Our findings suggest that a vast assortment of chemical exposures may initiate or escalate TILT/CI via chronic, aberrant MC activation.

### Similarities between MCAS and TILT

In Figs. 3, 4, 5 and 6, we see that the MCAS and TILT groups had statistically higher scores than did controls on the QEESI scales. We also see that the MCAS and TILT groups share strikingly similar patterns of symptoms and intolerances involving structurally diverse xenobiotics (chemicals, foods, and drugs).

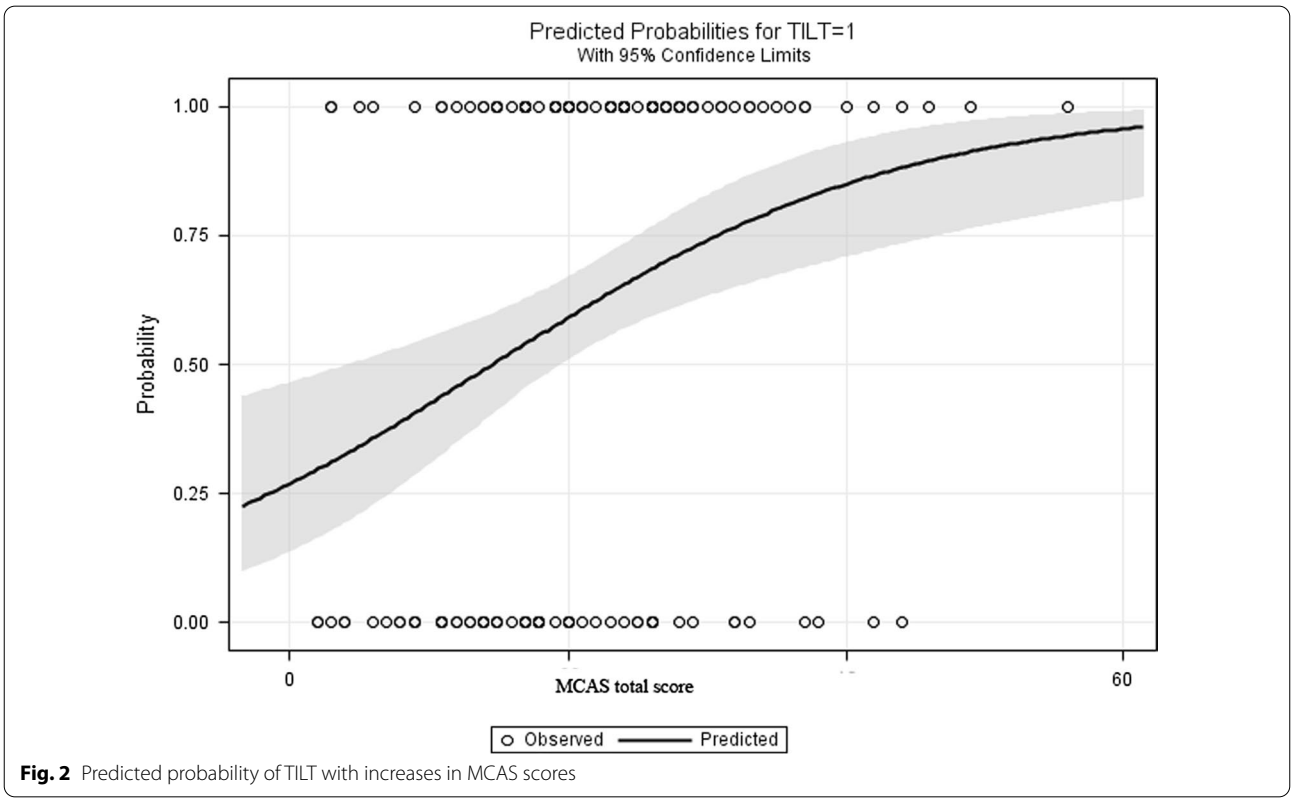


**Fig. 2** Predicted probability of TILT with increases in MCAS scores

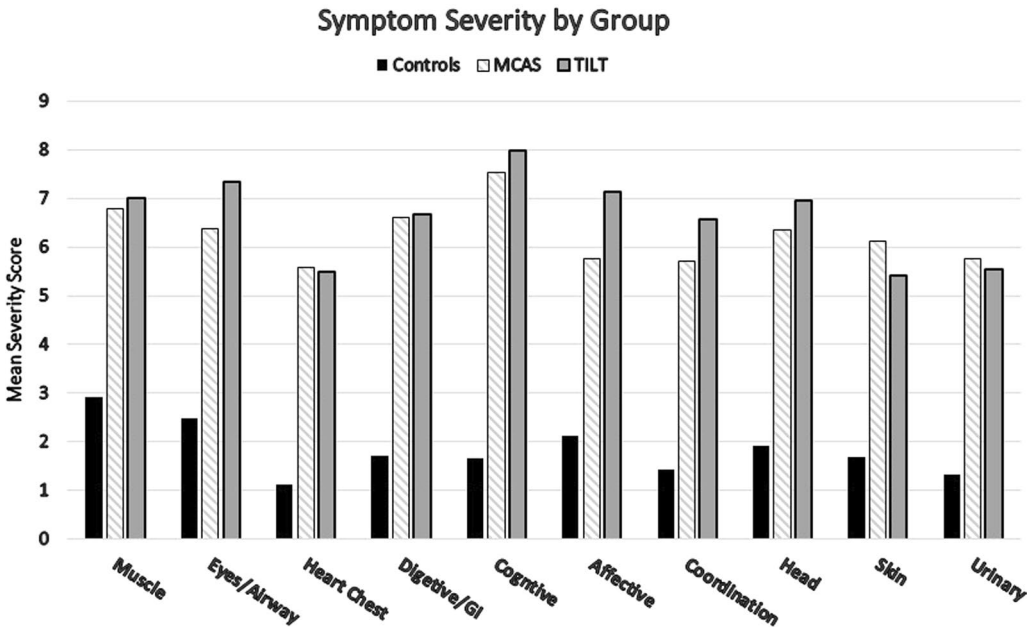


**Fig. 3** Distribution of QEESI Symptom Severity Scale items for TILT, MCAS and control groups

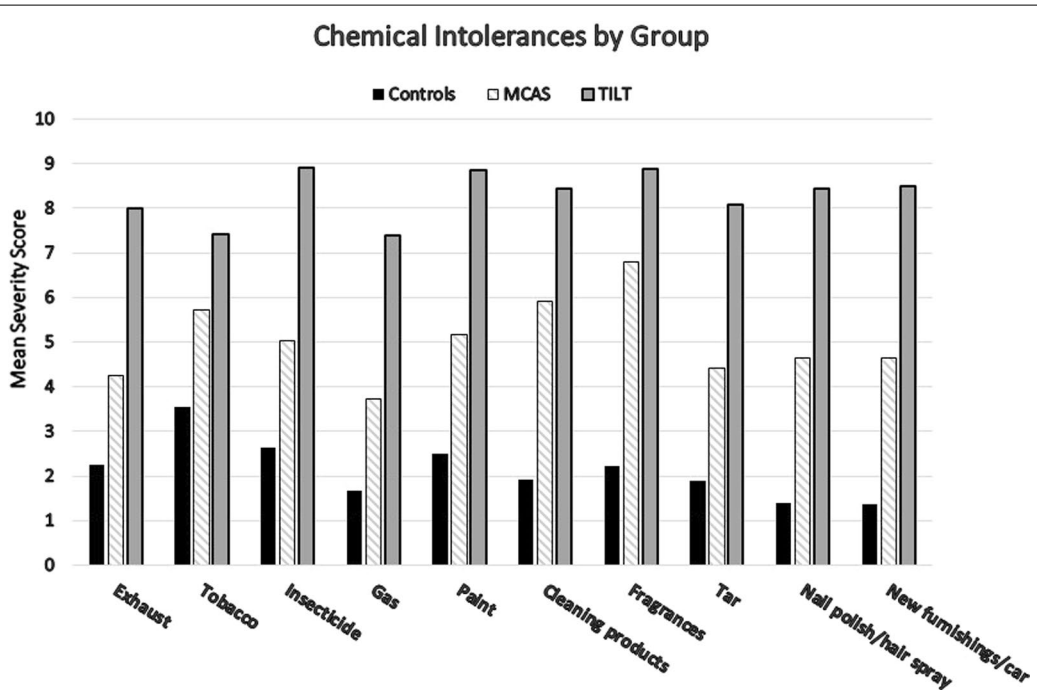


**Fig. 4** Distribution of QEESI Chemical Intolerance Scale items for TILT, MCAS and control groups

### *Symptom Severity Scale*

For most symptoms, there were significant differences between the MCAS and TILT groups. There was only a slight increase in severity in Affective and Neuromuscular symptoms in the TILT group compared to the MCAS group. Mediators released by MCs in the central nervous system may explain the neuropsychiatric symptoms patients in both groups commonly report.

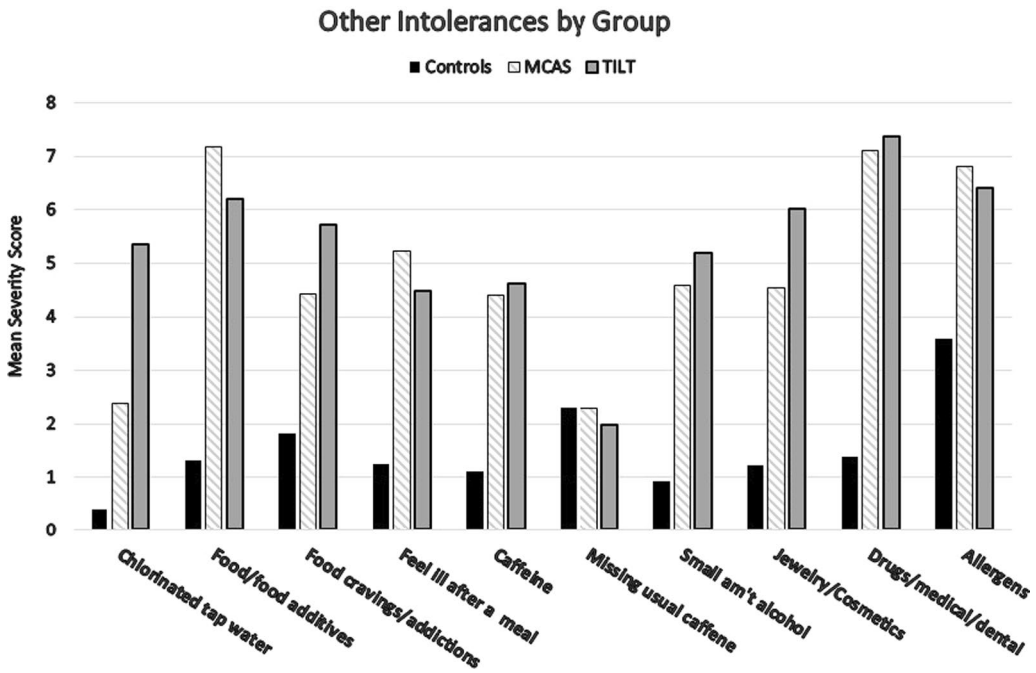


**Fig. 5** Distribution of QEESI Other Intolerance Scale items for TILT, MCAS and control groups

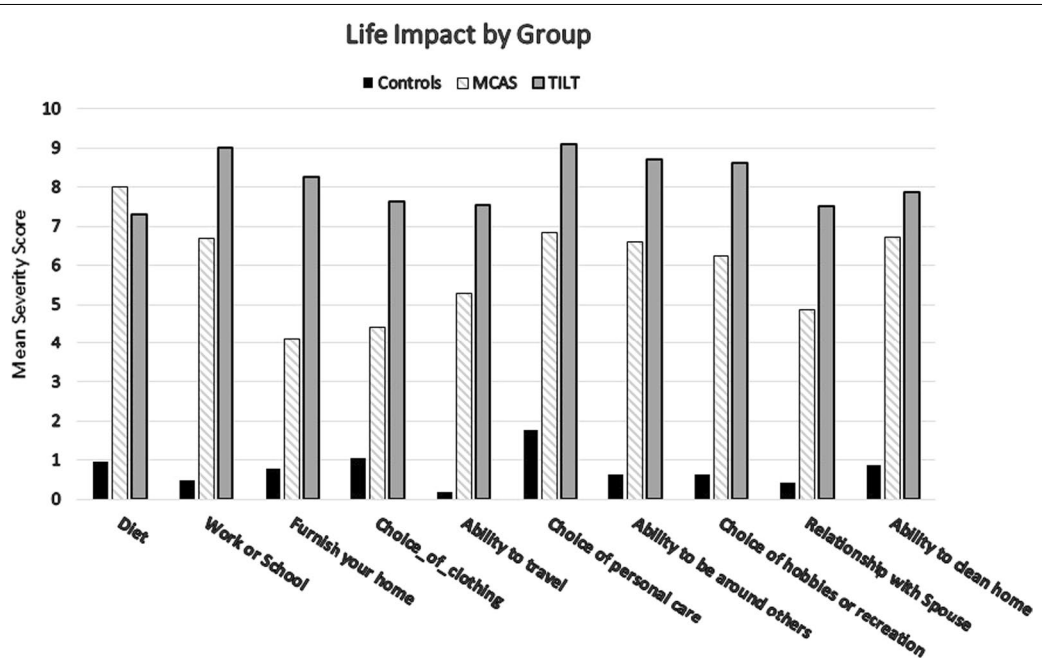


**Fig. 6** Distribution of QEESI Life Impact Scale items for TILT, MCAS and control groups

### *Chemical Intolerance Scale*

The same classes of chemicals appear to trigger symptoms in the MCAS group as in the TILT group, with the TILT group more severely affected. The most problematic triggers for many MCAS patients are fragrances (VOCs at extraordinarily low exposure levels), which also pose major problems for CI individuals [44].

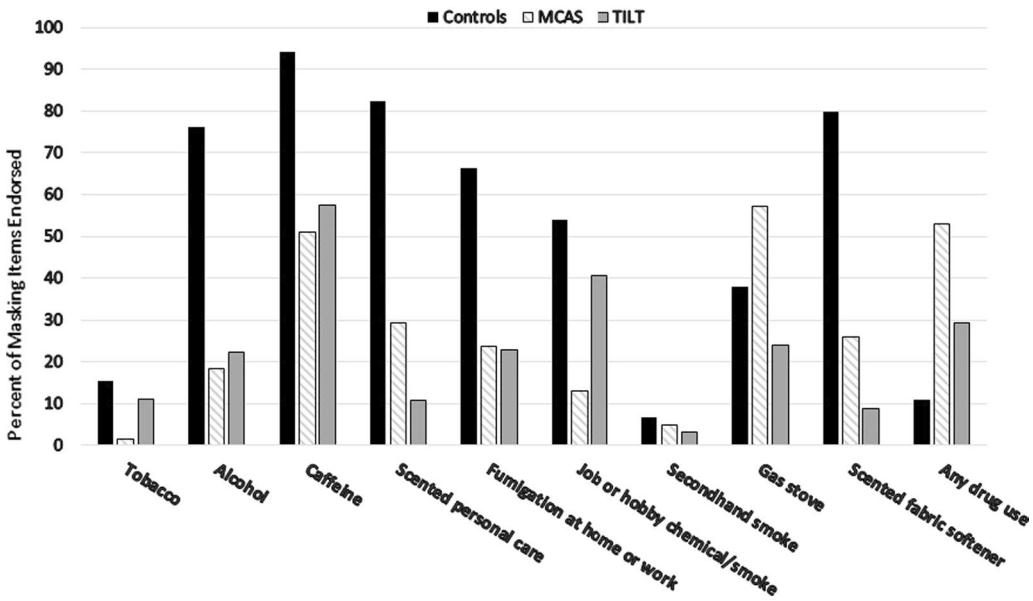


**Fig. 7** Distribution of QEESI Masking Index items for TILT, MCAS and control groups

#### *Other Intolerance Scale*

There were no significant differences between the TILT and MCAS groups for most of the items. Only the chlorinated tap water item was scored significantly higher by the TILT group.

#### *Life Impact Scale*

The TILT group consistently scored higher than the MCAS group on most of the Life Impact items. Individuals with TILT/CI may have greater difficulty tolerating exposures commonly encountered in social activities.

#### *Masking Index*

"Masking" can result from overlapping responses to chemicals as well as from an individual's tendency to habituate to these substances. Masking obscures the relationship between symptoms and chemical, food or drug triggers, literally hiding the cause-and-effect relationship between them from both patients and clinicians [45]. The control group endorsed more items on the Masking Index than did the TILT and MCAS groups, consistent with our prior studies [38, 46]. People without CI or MCAS may be more apt to use alcohol, tobacco products, and caffeine for their stimulatory effects to offset fatigue and brain fog. The MCAS group reported greater use of drugs/medications which could reflect the fact that MCAS is more commonly treated with medications to prevent MC degranulation and/or to block MC mediator effects. Many individuals with CI have experienced so many adverse drug reactions that they avoid most drugs, favoring alternative therapies such as herbs, homeopathy, or acupuncture [47].

### Connecting MCAS and TILT

Our understanding of the possible role for MCs in TILT is recent. Both patients with MCAS and those with TILT commonly report symptoms in multiple organ systems and often several systems simultaneously. MCs produce and release scores of chemical signals (generically termed "mediators") that can affect organs, tissues, and systems throughout the body.

TILT encompasses exposures which may have *initiated* illness, as well as exposures which continue to *trigger* symptoms. However, until now, TILT has lacked a clear biological mechanism, which MCAS may provide. An understanding of TILT's two stages, initiation and triggering suggests practical strategies for prevention and intervention, many of which also appear applicable to MCAS. Knowledge of the MCAS mechanism has the potential to inform new medical interventions and treatments for TILT. Failure to eliminate or reduce initiators such as pesticides or mold can result in chronic, even lifelong, illness in susceptible people, suggesting persistent MC activation and degranulation. The symptoms and findings in TILT patients may be best understood in the context of MCs and the mediators they release.

### MCAS, TILT, and the nervous system

Our proposal that MCAS could be the biological mechanism for TILT arises out of recent recognition that the spectrum of MC disease extends beyond clinically recognizable allergic phenomena (e.g., allergy, anaphylaxis, urticaria, angioedema, atopic dermatitis or eczema) and differs from the rare MC malignancy called "mastocytosis". Mastocytosis, first described in cutaneous form in the latter part of the nineteenth century and then in systemic form in the mid-twentieth century, manifests as chronic MCA resulting from neoplastic proliferation of MCs. Only recently, beginning in the 1980s, did researchers hypothesize the existence of MCAS [48, 49]. In 2007, the first case reports of MCAS appeared, describing patients with heightened release of MC mediators, yet without the excessive numbers of MCs which characterize mastocytosis. Many MC mediators have potent but short-lived effects. They are released locally in sensitized tissues and are exquisitely thermolabile, posing major challenges for measurement. MC's menagerie of mediators produce multi-system inflammation at minimum, and not uncommonly allergic-like phenomena, and sometimes aberrancies in growth and development (typically benign) in virtually any tissue.

As immunologic "first responders", activated MCs can initiate, amplify, and prolong wide-ranging neuroimmune responses [50]. Several investigators have pointed to neurogenic inflammation as a mechanism for CI [10, 51–53]. Rather than being the mechanism for CI, neuroinflammation may be the consequence of MCA and mediator release initiated by xenobiotic/chemical exposures. MCs affect neural function via their released mediators which bind with specific neuronal receptors [18, 54]. Also, MCs physically abut neurons in many tissues. Wherever such dyads are present, there is constant mediator "cross-talk" between the two cell types. Thus, MCA can provoke nearby neurons, inducing their associated symptoms; similarly, neurons can provoke nearby MCs, inducing their associated symptoms.

Correspondingly, quieting of MCs can help reduce neuronal activation, and, again, vice versa. [55]. Additional file 1: Table S1 lists selected MC mediators involved in neuroinflammation (after Theoharides et al. [56–59]. Many investigators have documented neuroinflammation and inflammatory mediators in CI [53, 60–62].

Both MCAS and TILT have prominent neurological features. For example, organophosphate pesticides, which bind irreversibly to cholinergic receptors in the parasympathetic nervous system, appear to be among the most severe and permanently damaging TILT initiators. Correspondingly, organophosphates have been shown to trigger degranulation in human and animal MCs [63]. The parasympathetic nervous system also modulates MC activity via a cholinergic pathway [64]. MCs play pivotal roles in regulating cerebral blood flow [65], directly affecting brain function. Notably, both MCAS and TILT patients commonly report cognitive difficulties which may be the result of reduced cerebral blood flow due to chemical exposures, such as vehicle exhaust or pesticides [66]. Brain MCs lie close to cerebral blood vessels, nerves, and the meninges, and inhabit the area postrema, choroid plexus, thalamus, hypothalamus, and limbic system, thus affecting memory, mood, and concentration. MCs can migrate between nerve tissue and lymphatics and appear to contribute to neuroinflammation in many disorders [67–69].

Notably, during stress, corticotropin-releasing factor is secreted by the hypothalamus, and, together with neurotensin, triggers MCs to release inflammatory and neurotoxic mediators, thereby disrupting the blood–brain barrier leading to neuroinflammation [70]. Referring to ADHD, Song et al. [55] cite increasing evidence that MCs are involved in brain inflammation and neuropsychiatric disorders. Selective release of inflammatory mediators by MCs, interacting with glial cells and neurons, may activate the hypothalamic–pituitary–adrenal axis and disrupt blood–brain barrier integrity.

This physiology of MCAS mirrors the two stages of TILT—initiation and triggering, that is, initiation by a single intense exposure, or repeated lower-level exposures (pesticides, implants, drugs, etc.), which immunologically sensitize MCs in the brain and/or other key sites. Thereafter, chemicals structurally related to the initiating event, as well as unrelated xenobiotic exposures, trigger mediator release by these pathologically "twitchy" MCs. Cognitive and mood effects can include sudden rage (e.g., "road rage"); impulsive, violent, or abusive behaviors; addictive tendencies; mental confusion/fatigue; and/or a sense of depersonalization. MC "twitchiness" renders these cells vulnerable to a host of unrelated exposures that never bothered the person before and do not bother most people. Therefore, it seems plausible that MC sensitization and triggering can explain both stages of TILT—initiation and triggering.

### Assessing and treating TILT/CI

Trigger identification and avoidance, rather than medications, are mainstays for treating CI. Likewise, these are the first steps for managing MCAS. Medications or desensitization procedures benefit many MCAS patients [31].

#### *Identifying and assessing TILT*

A systematic two-step evaluation works well for identifying patients with CI. First, administer the three-item Brief Environmental Exposure and Sensitivity Inventory

(BREESI) screener [39, 71] to help identify individuals with significant intolerances for chemicals, foods, and drugs. If one or more BREESI items are endorsed, the full QEESI is administered (http://tiltresearch.org/wp-content/uploads/sites/30/2017/05/qeesi.pdf). These instruments help identify initiators and triggers of CI. A detailed exposure/symptom history and timeline coupled with the QEESI can help identify environments needing specific assessment. Removing initiating exposures appears to be essential for sustained improvement among both TILT and MCAS patients. For both conditions, the QEESI Symptom Star, graphed based upon serial administrations of the QEESI over time, illustrates the dynamics of symptom severity as chronologically related to exposures [72–74] (see Additional file 1: S2).

Interestingly, the MCAS group reported greater use of gas stoves than did the TILT group (58% vs 25%, respectively), perhaps suggesting an important source and intervention for MCAS patients who use gas stoves. Historically, as early as the 1960s, removing gas appliances has been a principal recommendation for CI individuals [75].

#### *Dietary interventions*

Both TILT and MCAS patients report adverse reactions to foods. Most of these adverse food reactions are *food intolerances,* as opposed to immunoglobulin-mediated *food allergies,* e.g., to peanuts, discoverable through skin or blood testing. The gold standard for identifying food intolerances involves the rigorous elimination of suspect foods for 4 to 7 days, followed by judicious reintroduction of single foods, one-at-a-time, under close medical and dietary supervision. We recommend assistance from dieticians who understand food intolerances, food addiction, and elimination diets. Note that foods themselves may be triggers, but food additives and chemical residues on foods also are frequent triggers. Many CI patients opt for organic foods where available and affordable.

#### *Medical interventions*

After trigger identification and avoidance strategies are implemented, potential medical interventions for CI may include many of those used to treat MCAS, including agents that prevent MC degranulation like cromolyn and/or reduce tissue inflammation caused by MC mediators, such as H1 and H2 antihistamines administered *simultaneously* [31, 32, 76, 77]. Patients who respond adversely to excipients in commercially available medications may require compounded formulations. Interestingly, low-dose benzodiazepines help some MCAS patients due to the presence of benzodiazepine receptors on not only neurons, but also MCs [78, 79]. Pharmacotherapy for TILT/CI is by no means simple and requires minimizing exposures to chemicals known to precipitate adverse reactions and monitoring for inadvertent introduction of known triggers into the patient's regimen, such as when a different formulation is provided as a refill. These same challenges exist for MCAS patients.

#### *Other implications for clinical practice*

MC degranulation and mediator release offer an elegant explanation for TILT's numerous "unexplained" symptoms as well as for a host of so-called "idiopathic" illnesses sharing features of TILT. These include Gulf War Syndrome, breast implant illness, some mold-related illnesses, and various other exposure-induced conditions. Likewise, researchers and clinicians who wish to understand TILT-related or -overlapping conditions including fibromyalgia, chronic fatigue syndrome, depression, irritable bowel syndrome, asthma, eczema, attention deficit/hyperactivity disorder, or autism spectrum disorders [80, 81] need to take exposure histories which include asking when the illness began or was exacerbated, whether an initiating event occurred, and whether other people (or animals) were exposed or affected. Domestic cats for example are particularly sensitive to organophosphate pesticides [82]

### Study limitations

To the best of our knowledge, this is the first investigation of the similarities between MCAS and TILT, suggesting MCAS as a plausible mechanism for TILT/CI. However, symptomatic overlap between two study populations is not necessarily proof of a shared pathophysiology. Although an important strength of this study is that the QEESI (the reference standard for identifying CI) was used for all respondents, the MCAS and TILT/CI samples were approximately 20 years apart in data collection. This may introduce unknown historical biases. Additionally, the number of study participants was relatively small and unequal between the groups. Further, only gender and age were assessed and adjusted in the analysis. Other factors, such as medical history (e.g., asthma, obesity, other comorbidities), socioeconomic status, and other lifestyle variables could potentially bias the analysis. As such, these results should be considered preliminary until further studies can be conducted.

### Directions for future research and regulation

With this new understanding of the possible role of MCs in TILT, important questions arise concerning individual susceptibility differences that may be influenced by prior exposures, genetics, epigenetics, and nutrition.

Given the close parallels between TILT and MCAS, and the fact that MC activation and mediator release could explain much about TILT, future research should

address the following questions: (1) What proportion of the TILT population manifests detectable MC activation as determined by a rigorous diagnostic MCAS workup? (2) Do patients with TILT have somatic MC regulatory gene mutations as already found in many MCAS patients? (3) If so, are there *recurrent* mutations reflecting differing clonality patterns (e.g., in KIT) [83] characterizing differing subsets of TILT patients, perhaps even "fingerprinting" particular initiating exposures? and (4) Would specific treatments targeting MCs, or their mediators prove helpful for the TILT population as a whole or for certain subsets? As more research clarifies the role of MCs in TILT, targeted reduction of exposures can be implemented.

## Conclusion

Mast cell activation and mediator release appear capable of explaining the increasingly frequent observations by physicians and their patients of chronic multi-system symptoms and new-onset chemical, food and drug intolerances following exposure to a wide variety of xenobiotics. Our logistic regression model demonstrated that as the likelihood of patients having MCAS increases, their likelihood of having CI/TILT similarly increases, to a near-perfect correspondence at the high ends of these scales. Association is, of course, not proof of causation. Nevertheless, the strikingly similar symptom and intolerance patterns for the MCAS and TILT populations suggest that xenobiotics can disrupt mast cells, resulting in either or both of these challenging conditions. Faced with patients suffering from complex illness affecting multiple organ systems and fluctuating inflammatory, allergic, and dystrophic symptoms, researchers and clinicians should now ask themselves two questions: (1) Could MCAS be at the root of these problems? (2) Could xenobiotic exposures be driving MC activation and mediator release? Increasing our understanding of the connection between TILT and MCs has the potential to expose a new link between environmental exposures and illness, offering opportunities for improving individual and public health.

Almost daily, scientists, physicians, journalists, and the public are questioning whether toxic exposures of one sort or another are responsible for persistent symptoms reported following a wide variety of exposures including but not limited to the Gulf War, breast and other implants, the World Trade Center disaster, open burn pits, wildfires, pesticides, mold, and chemical spills and releases. Only in the last decade has knowledge of mast cells expanded to include mast cell activation syndrome (MCAS). MCAS mirrors the two-stage disease mechanism that Miller first described as toxicant-induced loss of tolerance (TILT) in 1996 [9], and we reported in a companion paper in this journal this year [7]—a mechanism we regard as a possible missing link between toxic exposures, multi-system symptoms, and loss of tolerance for chemicals, foods, and drugs.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12302-021-00570-3.

**Additional file 1: Table S1.** Representative examples of key mast cell mediators. **S2.** QEESI Symptom Star. Source: Miller and Prihoda [38].

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#### Authors' contributions

CSM conceived and designed this work. LA and TD provided insight and guidance regarding mast cells, and were responsible for the acquisition of the clinical data. RFP acquired the archived data, and analyzed and interpreted the statistical results. All authors contributed substantially to the drafting and revisions of the manuscript and approved the submitted version. All authors are responsible for the accuracy and integrity of the manuscript and data. All authors read and approved the final manuscript.

#### Authors' information

All authors have approved the manuscript before submission and have agreed to the order of authorship. We verify that all data and figures are compliant with the transparency and reproducibility standards of both the field and journal.

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#### Availability of data and materials

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Declarations

#### Ethical approval and consent to participate

This study was approved by the University of Texas Health Science Center San Antonio Internal Review Board (approval number HSC20150821H).

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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