



Exacerbating Factors in Chronic Spontaneous Urticaria

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Abbreviations CGRP Calcitonin gene-related peptide · CSU Chronic spontaneous urticaria · IL Interleukin · IFN Interferon

Abstract

Purpose of review Chronic spontaneous urticaria (CSU) is frequently associated with autoimmunity and is often exacerbated by several factors. These include stress, infections, colourings and preservatives in pre-packaged foods, as well as deficiency of vitamin D3 and iron. While chronic underlying infection and mental and emotional stress have been known to precede the onset of CSU, it is now clear that they can also aggravate the severity of the symptoms and perpetuate the condition. It is unclear how gastrointestinal dysbiosis affects CSU. Vitamin D3, however, can increase T regulatory function which can control a tendency to autoimmunity and inflammation. In this review, we discuss the different factors that can exacerbate established CSU, prolong the duration of the condition and encourage the need for second and third line therapy.

Recent findings While the precise molecular mechanism by which the above factors worsen CSU is unclear, there is some evidence that the Mas-related G protein-coupled X2 receptor (MRGPRX2) may be involved. This shows increased expression on the mast cells of patients with CSU and can be stimulated by anti-microbial host defence peptides, neuropeptides released during stress, major basic protein, eosinophil peroxidase and several peptidergic drugs. Several of these agents acting in concert may overcome the threshold for mast cell activation leading to CSU.

Summary CSU is a complex condition with multiple subthreshold aetiological factors frequently converging to effect mast cell activation. Effective treatment of CSU should

involve the use of anti-histamines, intermittent steroids and anti-IgE therapy. Depending on the clinical history, the 'talking therapies' that reduce stress and anxiety, vitamin D3 and iron supplementation, correction of intestinal dysbiosis and treatment of any chronic infection should also be considered.

Introduction

Chronic spontaneous urticaria (CSU) is a mast cell-driven condition. It is often defined as repeated urticaria evident for 6 or more weeks either continuously or intermittently. CSU has a lifetime risk of 20% and an annual prevalence of between 0.02 and 0.5% [1, 2]. It is now clear that CSU is 1.5 to 2.1 times more frequent in females. In just under half of all cases of CSU, the condition remains idiopathic with no evidence of organ specific and systemic autoimmunity or chronic infection, even after 10 years of follow-up [3]. In contrast to probable T helper (Th) 2 dominance in acute urticaria, there is no unique profile of T helper activity in CSU [4]. However, Th1, Th2 and Th17 cytokines have been reported to be elevated in CSU by Chen et al. [4], as well as reduced Th1 and Th17 cells with raised Tc1 and Tc17 by Lopes et al. [5] and increased pro-inflammatory cytokines and impaired T regulatory cells by Dos Santos et al. [6].

We have previously detailed several disorders which predispose to either CSU or mast cell irritability [7]. In addition to autoimmunity and autoimmune disease, there are several conditions which appear to frequently

co-exist with CSU and may be linked by a common underlying pro-inflammatory state. These are summarised in Table 1. However, there are also factors which can aggravate the frequency, extent and duration of the urticarial wheals and which if treated or attenuated can ease the symptoms of CSU. In this regard, raised stress levels, ingestion of one or more pseudoallergens such as colourings, preservatives and salicylates and variation in the activity of any underlying or coincidental infection appear important. Alterations in bowel permeability in response to changes in gastrointestinal microbiota may also be relevant in a small number of patients, but further work is needed to conclusively establish this. Although IgE-mediated food allergy is rarely a cause of CSU [8], and more frequently represents inducible urticaria, the frequency of associated atopy is increased and the severity of the condition can vary with atopy symptoms [9]. In the present report, we discuss the role of pseudoallergens, autoimmunity, infection, gastrointestinal dysbiosis, stress and atopy as aggravating factors in established CSU.

Factors that aggravate established CSU

Pseudoallergens

The debate regarding the importance of low molecular weight preservatives, colourings, salicylates and histamine in CSU has continued for many years. In the case of salicylates, a plausible mechanism for worsening of CSU is based on cyclooxygenase 1 inhibition causing an altered prostaglandin/leukotriene ratio [10, 11]. However, IgE is not involved in this process and there is little or no evidence that pseudoallergens can act as haptens and thereby lead to heightened allergic immune reactivity.

In some patients, the dietary reduction or elimination of preservatives, colourings and salicylates has significantly reduced CSU activity [12•, 13•, 14, 15•]. This was accompanied by reduced urinary leukotriene E4

Table 1. Conditions that aggravate CSU and outline of possible underlying mechanism. Adapted from Bansal, C.J., Bansal, A.S. Stress, pseudoallergens, autoimmunity, infection and inflammation in chronic spontaneous urticaria. *Allergy Asthma Clin Immunol* 15, 56 (2019). <https://doi.org/10.1186/s13223-019-0372-z>, under Creative Commons Attribution 4.0 International License

Variable	Outline of purported mechanism
Autoimmunity	Female predominance is evident in both systemic and organ-specific autoimmunities and CSU. The positive autologous serum skin test is frequently associated with underlying autoimmunity and altered T cell subsets. Autoreactive IgE and IgG antibodies are common in CSU, and removal of former with anti-IgE therapy suggests direct ability of IgE autoantibodies to activate mast cells.
Pseudoallergens	The mast cell Mas-related G protein-coupled receptor X2 may be directly stimulated by the low molecular weight colourings, preservatives and additives or they lower the threshold for other factors to fully activate the mast cells to release CSU mediators. In predisposed people, salicylates and non-steroidal anti-inflammatory drugs increase overall leukotriene activity by COX-1 inhibition leading to mast cell activation and further CSU activity.
Stress	Stress induces the release of several neuropeptides that can activate mast cells via Mas-related G protein-coupled receptor X2. Stress can also impair T regs function leading to dysregulated T and B cell control with increased tendency to autoimmunity and inflammation.
Infection	Parasites excite humoral autoimmunity especially a polyclonal IgE which may have autoreactive components. Gut infection may also increase epithelial permeability allowing the entry of bacterial components and low molecular weight pseudoallergens.
Atopy	Much of work here is in children but anything which stimulates the immune system worsens CSU. Atopic patients also have raised IgE levels and a proportion of these may be autoreactive.
Iron deficiency	How iron deficiency worsens CSU is unclear, but iron supplementation can be helpful in some such patients.
Hormonal variation	CSU described to be worse with uncontrolled thyroid dysfunction and pre-menstrually in women. In both cases, appropriate hormonal treatment can be helpful. Unclear whether increased stress mediates the worsening of CSU in these conditions.
Dysbiosis of gastrointestinal tract	Altered populations of several types of stool bacteria are evident CSU. These alterations may promote increased gut epithelial permeability and absorption of immune stimulating compounds as well as affecting gastrointestinal tolerance mechanisms.
Vitamin D3	Reduced serum levels evident in CSU. Vitamin D3 reduces Th1 and Th17 cells and increases T regulatory cell function that can diminish autoimmunity and lower inflammation.

excretion [12•], but provocation testing with 'known food dyes and preservatives' was positive in only 18% of the 73% of CSU patients originally responding to the pseudoallergen-free diet [16]. Similarly, Rajan and colleagues found only 2 of their 100 patients with CSU reacted to a single blind challenge with 11 of the most frequently used additives [17]. Interestingly, intestinal permeability has been noted to be raised in patients with CSU and was partly reversed by 24 days on a low pseudoallergen diet [18•]. Thus, CSU may require a combination of temporary pseudoallergen sensitivity and increased gut permeability. In the case of dietary histamine and its impact on CSU, Son et al. reported an improvement in urticarial activity with a low histamine diet in 22 patients with CSU [19]. Plasma histamine levels were higher before the low histamine diet, but it is unclear whether the spontaneous improvement that is seen to occur in CSU could, in part,

explain the results.

Autoimmunity

There is now incontrovertible evidence that autoimmunity and autoimmune diseases are more frequent in patients with CSU. This is particularly true for IgG anti-thyroid peroxidase antibodies and hypothyroidism [20–22]. However, type 1 diabetes, rheumatoid arthritis and Sjogren's syndrome are also increased in those with CSU [23•]. In this respect, a positive autologous serum (AST) or plasma test (APT) in 40 to 60% of patients with CSU has always suggested the presence of mast cell stimulating autoantibodies [24]. Importantly, a positive AST has been reported to increase the progression of acute spontaneous urticaria to CSU [25] and a reduced chance of spontaneous resolution over 2 years [26]. Moreover, IgG antibodies directly able to bind to the FcεRI and with the potential to activate mast cells have been detected in almost a quarter of patients with CSU but only 3.2% of healthy controls [27]. Interestingly, IgE anti-TPO antibodies are also evident in CSU which suggests one of the possible mechanisms of action behind anti-IgE therapy in CSU [28, 29•].

Clinically, the severity of CSU appears to be increased and with difficulty controlling the condition with anti-histamines alone in those with uncontrolled hypo- and hyperthyroidism. Overall, the consensus is that thyroxine replacement therapy can be helpful to control CSU and reduce the need for second line therapy. Additionally, reducing excessive thyroid function has been shown to improve CSU control in those with hyperthyroidism [20].

Infections

While a variety of viral [30, 31•], bacterial [32], fungal [33] and helminth [34] infections have been reported to precipitate the onset of CSU, there is less evidence that new infection in those with established CSU worsens the condition. One of the infections receiving most attention in CSU is *Helicobacter pylori*; however, its role in precipitating and/or aggravating the condition remains unclear. Recent work suggests asymptomatic infection to be more frequent in individuals with CSU than healthy controls and the urticaria to be more severe and extensive in helicobacter positive patients [35]. Interestingly, the LAD2 mast cell line stimulated by a 23- to 35-kDa protein from helicobacter preparations was found to induce the release of histamine, TNF-α, IL-3, IFN-γ and leukotriene [36]. Mechanistically, inflammatory cytokines such as IL6 promote an increase in human mast cell numbers and reactivity through a suppression cytokine signalling [37•]. In this regard, it is relevant that raised levels of IL6, IL1β and TNFα with the ability to stimulate mast cells have been reported in patients with infection and in CSU [38].

In reference to the gastrointestinal microbiota, there has been recent interesting work showing an increased prevalence of dysbiosis of the gastrointestinal tract in CSU. More specifically, this comprised a markedly reduced occurrence of *Akkermansia muciniphila*, *Clostridium leptum* and *Faecalibacterium prausnitzii* in the stools of CSU patients, while the frequency of *Enterobacteriaceae* was unchanged [39]. Furthermore, the 'relative

amounts' of faecal lactobacillus and Bifidobacterium was lower in patients with CSU compared to health controls [40]. Interestingly, the number of CD117 and tryptase positive mast cells per high power field was pointedly higher in patients with CSU compared to controls, and treatment with mast cell stabilisers has been suggested [39]. With these facts in mind, it is possible that antibiotic therapy, for reasons other than the CSU, may have the potential to alter the microbiota and produce variable degrees of either improvement or worsening in the CSU. Conversely, some CSU patients have found probiotics helpful [41].

Stress and altered mood

A high proportion of patients with CSU note significant worsening of their condition with raised stress levels. Conversely, the unpredictability of urticarial episodes in CSU can lead to persistent stress [42•]. Importantly, several reports have now confirmed CSU patients to have a significantly higher frequency of depression, anxiety and poor quality of sleep [1] that is associated with a reduced quality of life [43, 44]. In at least one report, there was a significant correlation between levels of depression and anxiety assessed using the Hospital Anxiety and Depression Scale and urticarial activity [45]. Overall, there is increasing evidence that continued stress can perpetuate and aggravate CSU, and high levels of stress can predispose patients to developing CSU [46].

The mechanism by which CSU is worsened by stress is presently unclear. However, it is interesting that the basophils in those with CSU appear to activate more readily with adrenocorticotrophic hormone and corticotrophin releasing factor, compared to healthy controls [47•]. Additionally, there is a probable molecular association between mast cells and nerves with certain neuropeptides, but especially substance P, capable of stimulating mast cells to release histamine and the other mediators in CSU [48•]. Intriguingly, several neuropeptides such as vasoactive intestinal peptide, α -melanocyte-stimulating hormone and calcitonin gene-related peptide (CGRP) have been found in the central nervous system as well as being released locally by cutaneous nerves [49, 50]. Immunologically, CGRP appears to encourage Th17 type cells with the potential to increase inflammation through the recruitment of T cells and neutrophils [49, 51]. Moreover, stress leading to the release of sensory nerve neuropeptides can also alter the behaviour of dermal Langerhans cells to stimulate specific T helper cell pathways [51]. At a biochemical level, stress may stimulate the local release of substance P and CGRP by sensory cutaneous nerves, leading to mast cell activation and subsequent itching via one or more receptors. This activation would include the Mas-related G protein-coupled receptors (Mrgpr) family as well as transient receptor potential ankyrin 1 (TRPA1) and protease activated receptor 2 (Par2) [49]. Activated mast cells would subsequently release several important cytokines but especially IFN- γ , IL-4, TNF- α and IL-10 which in turn may encourage further immune activation and the worsening of cutaneous inflammation.

This has the potential to perpetuate the itch-scratch cycle much in the same way as in atopic dermatitis.

Vitamin D3 and iron

Vitamin D3 (cholecalciferol) deficiency is frequent in the Western world and areas with limited sunshine [52]. However, vitamin D3 is important not only in bone mineralisation but also in immune function and can increase T regulatory cell function and reduce Th1 and Th17 type immunity [53]. These changes improve the control of autoreactive B and T cells, and reduced serum vitamin D3 has been found in many of the systemic autoimmune diseases [54], asthma [55] and inflammatory bowel disease [56]. Importantly, reduced serum vitamin D is found more frequently in CSU than in healthy controls [57–59] and supplementation reported to be beneficial in ameliorating the severity and duration of the urticarial wheals [60, 61].

Iron deficiency has anecdotally been associated with CSU and iron supplementation found to be helpful in a proportion of such patients. In one report of Italian patients with poorly controlled CSU and moderately low serum iron levels, a 30- to 45-day course of oral iron replacement therapy produced complete remission or an 80% or more improvement in their symptoms [62]. Another group recorded significantly lower ferritin levels in their cohort of > 1500 CSU patients compared to the general population. Interestingly, this difference was no longer present when adjusted for female gender, suggesting that ferritin deficiency may only be important in the pathogenesis of CSU in men [63].

Atopy

Atopic conditions such as eczema, asthma and seasonal allergic rhinitis are both frequent and with a rising incidence. Much of the work linking atopy and CSU has been in children. Here the association between atopy and childhood urticaria has been more strongly defined than in adults, and CSU is a significant risk factor for allergic rhinitis in children, as well as commonly occurring with atopic dermatitis in infants [64, 65]. However, any form of atopic disease was noted in 52.7% of a large cohort study of CSU patients, and evidence of sensitisation through skin prick testing to more than one common nutrient or inhalant allergen was seen in 39.1% of individuals [66].

The link between atopy and CSU can also be extrapolated from the mechanism of action of first line treatments for this condition. Thus, anti-histamines used in both conditions work by reducing the levels of pro-inflammatory mediators of mast cell activation [67]. Similarly, the relationship between atopic disease and urticaria may be inferred from the benefit of anti-IgE therapies such as omalizumab. Here, it has been anecdotally noted that patients who have a good response to omalizumab have higher total IgE levels than those who do not respond. Furthermore, the atopic status of a patient with CSU can be an influencing factor in the ability of IgE to predict the success of omalizumab therapy. This in turn raises the possibility of raised

aberrant autoreactive IgE activity in those with elevated total and specific IgE and particularly in the subgroup of patients who respond well to anti-IgE therapy atopy [68].

Hormonal variations

The prevalence of CSU is known to be higher in females compared to men. This is also the case with systemic and organ specific autoimmune disease. Intriguingly, the severity of CSU in some women can correlate with variations in their sex hormones during the ovarian cycle [69]. Additionally, a woman with severe urticaria and significant peri-menstrual worsening found her symptoms resolved after the introduction of oral contraceptive agents [70]. Similarly, a young woman with pre-menstrual worsening of her CSU and positive skin prick testing to progesterone was markedly improved by a gonadotropin-releasing hormone (GnRH) analogue [71]. While there appears to be progesterone autoreactivity here, the precise mechanism linking oestrogen and progesterone and CSU is unclear although autoimmunity and premenstrual stress are two obvious candidates.

Linking the different factors that can aggravate CSU

While seemingly diverse, the several factors that can aggravate CSU may be linked via a common pathway. Thus, autoreactivity and autoimmunity have been linked to stress [72–77], and viral infections, such as Epstein Barr, are well known to encourage autoimmunity [78, 79]. In brief, this involves a combination of impaired T regulatory function and viral proto-oncogenes that support the survival of low avidity autoreactive B cells which are normally eliminated. Stress can also increase the permeability of the gastrointestinal epithelium [80] and thus increase the absorption of low molecular compounds of dietary and microbial origin. These may then stimulate mucosal mast cells to release inflammatory factors and the mediators involved in type 1 hypersensitivity. Consequently, certain infections and stress may be linked to an increased susceptibility to CSU by perturbation of the immune system.

Mechanistically, the different aggravating factors for CSU detailed above may be linked by the Mas-related G protein-coupled X2 receptor (MRGPRX2) that is present on mast cells and which was previously known as MrgX2. As such, it is pertinent that increased expression of these receptors has been reported on the mast cells of patients with CSU compared to healthy controls [81••]. Crucially, MRGPRX2, can be stimulated by 'antimicrobial host defence peptides such as β -defensins and the cathelicidin LL-37 [82•], neuropeptides such as substance P [81••] and vasoactive intestinal peptide, major basic protein, eosinophil peroxidase, and several peptidergic drugs' [83•, 84]. This raises the prospect that several of these factors at subthreshold level acting in concert may collectively lead to mast cell degranulation and CSU. As an example, a routine infection attended by the upregulated secretion of anti-microbial defence peptides

and on a background of high stress with raised consumption of foods with preservatives and colourings may collectively precipitate urticaria although each factor in isolation may be unable to do so. Additionally, the capriciousness of CSU can create and/or aggravate stress which then perpetuates the urticaria even when the original infection has been eradicated and there has been an improvement in the diet.

Therapeutic relevance of autoimmunity, pseudoallergens, stress, low vitamin D, iron and infection in CSU

The interaction of the more important factors that impact on CSU is shown in Fig. 1. Many of these are interlinked, and the holistic treatment of CSU requires attention to all these factors in addition to appropriate treatment with second generation anti-histamine therapy as suggested by the European and World Allergy Organisation guidelines on urticaria [85•]. In general, many CSU patients with readily controlled CSU do not require investigation [85•]. However, those not responding to standard therapy with high-dose anti-histamines should be investigated for significant stress preceding or accompanying the CSU and in addition for overt or occult infection. Other factors needing consideration include underlying serological or clinical autoimmunity, iron deficiency, low levels of vitamin D, gastrointestinal dysbiosis and *Helicobacter* infection [86]. In this case vitamin D3, probiotics, anti-microbials, oral iron therapy and levothyroxine may prove advantageous [87]. In the case of colouring and preservative free diets, these may be worth considering on a temporary basis and depending of a dietary assessment of the amount of

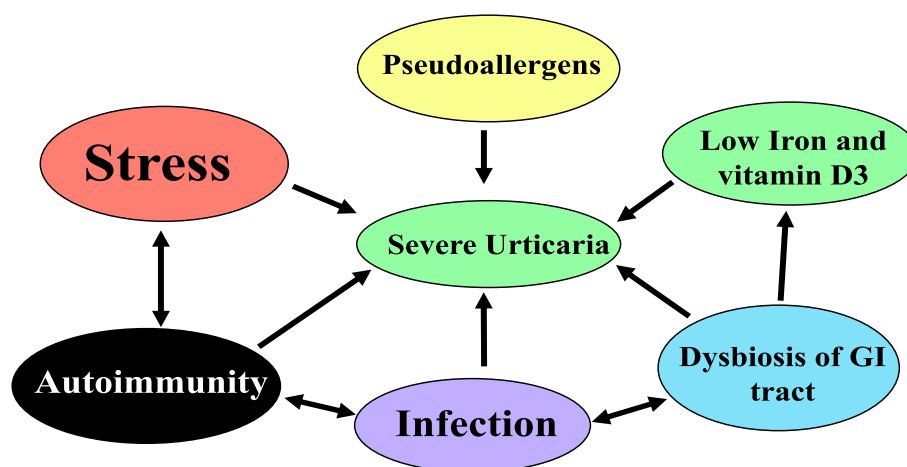


Fig. 1. Inter-relationship between the various factors that can aggravate CSU. Adapted from Bansal, C.J., Bansal, A.S. Stress, pseudoallergens, autoimmunity, infection and inflammation in chronic spontaneous urticaria. *Allergy Asthma Clin Immunol* 15, 56 (2019). <https://doi.org/10.1186/s13223-019-0372-z>, under Creative Commons Attribution 4.0 International License.

pre-packaged food consumed.

Stress reduction is an important part of the management of all patients with CSU as it can precipitate, aggravate and perpetuate the condition but may require specific questioning to uncover any obvious sources [42•, 88]. Once identified as significant, stress reduction therapy using a variety of approaches should be implemented early to limit morbidity and improve overall quality of life [89].

Conclusion

The threshold for developing CSU is reduced by several common conditions while others frequently modify the severity of the urticarial wheals or prolong the duration of the CSU. These conditions are associated with impaired immune regulation and/or an underlying pro-inflammatory state that can contribute to mast cell irritability and an increasing tendency to autoimmunity. The latter is often directed towards IgG and IgE cell surface receptors. Persistent stress and mild underlying infection can be associated with the release of several neuropeptides and anti-microbial host defence proteins. Acting through the intermediacy of the MRGPRX2 receptor, these can lower the threshold for mast cell activation and worsening of CSU. All factors known to affect urticaria should undergo clinical and laboratory investigation to provide a tailor made holistic management protocol specific for each CSU patient. In the long term, this should minimise the severity and duration of the CSU with a reduced requirement for second- and third-line therapies.

Authors' contributions

Conceptualisation by RAB and ASB. RAB wrote the first draft. Both authors have reviewed the manuscript prior to submission. Data availability Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Compliance with ethical standards

Conflict of interest

Rhea Bansal declares that she has no conflict of interest. Amolak Bansal declares that he has no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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