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# Chronic spontaneous urticaria: from the hunt for causes and pathogenesis to the identification of different endotypes

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## KEY WORDS

*Chronic urticaria; autoimmunity; autoallergy.*

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## Summary

*The hunt for the causes and pathogenic mechanisms involved in chronic spontaneous urticaria (CSU) has engaged clinicians and scientists for decades. Although not all aspects of the disease are defined, our knowledge has now improved to the point that we can consider CSU as an umbrella clinical phenotype under which several different endotypes probably exist. The present article will briefly summarize the fascinating history of the progress in our knowledge of this disease.*

## IMPACT STATEMENT

*Chronic spontaneous urticaria is an umbrella term encompassing several disease endotypes showing an identical phenotype. These include autoimmunity, autoallergy and other pathogenic mechanisms that are emerging overtime.*

## Introduction

Chronic spontaneous urticaria (CSU), defined as the spontaneous occurrence of itchy wheals with or without angioedema for more than six weeks (1), is a rather common disease affecting at least 1% of the general population at a certain time point. It has been estimated that more than 50 million people are affected by CSU all over the world. The disease, especially when it presents in a severe form, may heavily interfere with most of everyday activities, including sleep, school and work performance, and social relationships, and

negatively influence self-esteem, thus worsening severely the quality of life (2, 3). Although the role of histamine and of several other proinflammatory cytokines released by skin mast cells and basophils in wheal formation is unquestioned, several aspects of the pathophysiology of CSU still remain unclear. Nonetheless, the last 75 years have witnessed great advances in our understanding of many of the mechanisms underlying the disease. The present article will try to summarize in a short history following both a chronological and a thematical order the long way that has led us where we presently stand.

### The autologous serum skin test: birth of the concept of autoreactivity

The first step towards the concept of autoreactivity was made in 1946, when Malmros investigated the effects of the intradermal injection of autologous serum in 956 patients with different disorders, recording a wheal-and-flare reaction in 53 patients, 16 of whom with asthma and 6 with urticaria (4). The idea of the presence of autoreactivity in CSU, broadly encompassing the concept of pathological reactions to endogenous signals, received a decisive impulse more than 30 years ago, when Grattan and co-workers (5) demonstrated that a significant proportion of CSU patients show a positive autologous serum skin test (ASST), thus prompting the existence of circulating histamine-releasing factors in this disease. A number of following studies confirmed these observations although the prevalence of positive ASST varied greatly from one study to another, probably due to differences in populations, testing techniques, and selection of patients (6). Nonetheless, these studies taught that a proportion of chronic urticaria patients (about 40-50% is a generally accepted figure) show autoreactivity (7, 8), a concept that was enforced by an EAACI consensus taskforce more than one decade ago (9). However, conversely, this also means that no sign of autoreactivity can be detected in a large proportion of CSU patients. Regarding the specificity of the ASST, several studies carried out over the years demonstrated that also patients with conditions other than CSU, including chronic inducible urticarias such as cold urticaria, multiple drug allergy syndrome, and multiple hypersensitivity to nonsteroidal anti-inflammatory drugs may score positive on the intradermal injection of autologous serum (10-12). Interestingly, all these conditions are to some extent associated with urticaria. The autologous plasma skin test (APST) was found to score positive more frequently than the ASST in CSU patients (13). This finding was confirmed by several (but not all) independent authors; nonetheless, apart from its potential usefulness as a more sensitive means to detect an autoreactive state, the major merit of APST was to give the start to the study of coagulation in CSU (see beyond).

### The discovery of an autoimmune pathogenic mechanism in CSU

The observation that many CSU patients score positive on ASST prompted the scientific community to look for circulating histamine releasing factors. In effect, some years after the pioneer research by Grattan and co-workers (5), different studies demonstrated the occurrence of functionally active IgG autoantibodies that were directed against mast cell membrane-bound IgE in a minority of cases and the high affinity IgE receptor, (FcεRI), in a larger proportion of patients (14-17). Later studies found that this pathogenic mechanism, that is currently known also as type

IIB CSU following the Gell-Coombs classification (18), can be mediated also by IgM or IgA autoantibodies (19). One problem that appeared soon was that, although this was a fascinating explanation for the ongoing histamine release, it could in fact be detected only in a minority of patients (8, 15, 16, 20). Another point was that both types of autoantibodies have been detected with similar frequencies in subjects with and without CSU (20). Nonetheless, more recently, the autoimmune pathogenesis has been further supported by the detection of circulating autoreactive CD4<sup>+</sup> T cells that proliferate in response to FcεRI in > 50% of CSU patients (21). Further, one recent international study investigated the clinical features of patients with “true” autoimmune chronic spontaneous urticaria selected on in the basis of three precise criteria (positive ASST, positive *in vitro* test of basophil activation – either basophil activation test (BAT) or basophil histamine release assay (BHRA) –, and presence of autoantibodies to FcεRI or IgE) (22). It turned out that the relatively few (8%) patients fulfilling all three criteria showed a specific picture characterized by more severe disease, lower total IgE levels, and higher IgG anti-thyroid peroxidase (TPO) levels. The much larger proportion (58%) of patients scoring positive for IgG anti-FcεRI or IgE who were considered as having a “partial” aiCSU showed higher IgE levels, lower thyroid peroxidase IgE and a less severe disease than patients with a “true” aiCSU.

### Autoreactive (ASST+) and autoimmune (type IIB) CSU: correlations and differences

One point has been clear over the years: the ASST (a marker of autoreactivity) and autoimmune CSU are somehow associated but not overlapping. In a study of > 300 CSU patients (8) the ASST scored positive in > 60% of patients but sera from only 16.5% were able to induce histamine release from basophils of normal donors on the BHRA (basophil histamine release assay), considered as a marker of the presence of functionally active autoantibodies (8). Interestingly, all BHRA+ patients were ASST+, but only 22% of ASST+ patients were also BHRA+. In BHRA+ patients, serum fractions > 100 kDa fully retained the *in vitro* histamine-releasing ability, whereas serum fractions < 100 kDa were inactive on donors' basophils. In another study (23), heat-decomplemented/IgG-depleted sera from ASST+ CSU patients were still able to elicit a wheal-and-flare reaction on intradermal testing. The basophil activation test (BAT) and the ASST did not show a significant correlation in some studies (24, 25), although in another, more recent one (22) ASST-positive patients included virtually all BAT+ patients, whereas much more discrepancy existed between ASST and IgG anti-FcεRI or anti-IgE.

One surprising observation is that heparin inhibits the intradermal skin test both when autologous heparinized plasma is employed and if heparin is added to autologous serum or

serum is adsorbed with solid phase heparin (8, 26). The inhibiting effect was observed also *in vitro* (8), possibly due to a direct action at a cellular level. Another interesting observation is that antihistamines exert little inhibitory effect on intradermal test with autologous plasma anticoagulated with sodium citrate (27). Altogether the serum and plasma factors causing a positive wheal-and-flare upon intradermal injection in CSU patients remain insufficiently characterized (28).

### Autoimmune diseases are associated with CSU

The association between CSU and thyroid autoimmunity has been known for many years (29), and several studies were able to demonstrate that the prevalence of a variety of autoimmune disorders, including autoimmune thyroiditis and vitiligo, is higher in CSU patients than in the general population (30-36). In a study of > 1,100 patients with CSU (36), 28% had one or more comorbid autoimmune disease. Along with thyroid autoimmunity and vitiligo, also rheumatoid arthritis, autoimmune gastritis, and ankylosing spondylitis showed a higher prevalence among patients than in the general population. The autoimmune origin of a proportion of cases of CSU has been confirmed by immune-genetics studies showing an association with HLA Class II antigens frequently involved in autoimmune diseases (37), and recently by a genome-wide association study (38).

### Autoallergy: the other side of the moon

As seen before, histamine-releasing IgG autoantibodies could be detected in no more than one fourth of CSU patients, leaving three quarters of patients without a reasonable explanation for their disease. The story changed completely at the end of the last century when the first case of IgE to thyroid peroxidase was published (39). This finding was confirmed more than one decade later (40) and provided a rationale for the use of omalizumab in H1-antihistamine resistant CSU. The initial observations of Spector *et al.* (41) on the beneficial effect of omalizumab in three patients with CSU refractory to conventional treatment together with the demonstration of autoreactive IgE led to the first controlled clinical trials on the use of omalizumab in H1-antihistamine resistant CSU (42, 43). Subsequent studies found that CSU patients' sera may contain IgE specific for a large variety of auto-allergens including interleukins (particularly IL-24), dsDNA, tissue factor, thyroglobulin, eosinophil cationic protein, eosinophil peroxidase and FcεRI (44-48). *In vivo* studies demonstrated the functional relevance of TPO IgE autoantibodies showing that in CSU patients with high IgE-anti-TPO levels skin testing with TPO induced a wheal-and-flare reaction (49). Further, the passive transfer of IgE-anti-TPO from a CSU patient to the skin of a normal subjects was associated with the appearance of skin reactivity to TPO in the receiving

subject (49). All these observations led to the concept of auto-allergic CSU that is currently also called type I CSU following the Gell and Coombs classification (18). Whether the ASST, a marker of autoreactivity (9), may be helpful in distinguishing between type I and type IIb CSU has not been well defined yet (28), and is currently being studied. Data from previous studies (22) suggest that this might not be the case.

### Autoallergic (Type I) and autoimmune (Type IIb) CSU may co-exist

There is increasing evidence that the two autoimmune mechanisms detected in CSU patients are not mutually exclusive. In fact, several studies showed the co-existence of IgG and IgE autoantibodies directed against the same targets (48-52). Interestingly, the presence of IgG autoantibodies appears to influence the clinical response to anti-IgE treatment (51).

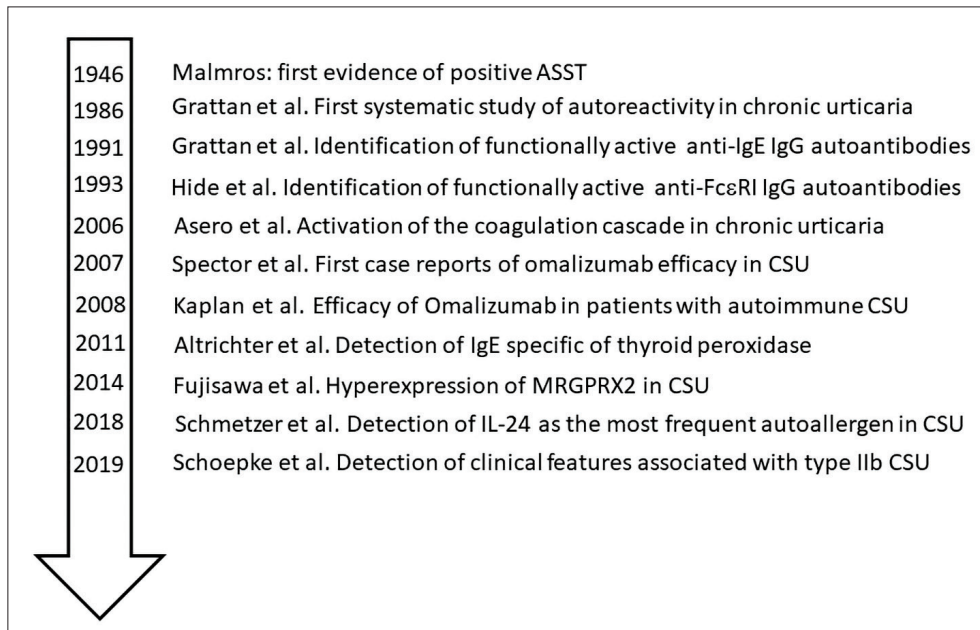
### CSU as an inflammatory disease

Although the classical markers of systemic inflammation that are employed in clinical practice such as erythrocyte sedimentation rate or C-reactive protein score most often normal in patients with CSU, there has been increasing evidence that the disease is characterized by a systemic pro-inflammatory state. The enormous number of studies showing increased levels of different single markers of inflammation (*e.g.*, matrix-metalloproteinase-9, eosinophil cationic protein, complement, tumor necrosis factor-alpha, IL-18, and others) that have appeared in the medical literature over the years will not be reviewed in detail here. What is interesting to note is that the levels of many of these markers show an association with disease severity (53-56). A typical example in this sense is the activation of the coagulation cascade via the extrinsic pathway (57) following the hyper-expression of tissue factor by activated eosinophils (58) or endothelial cells (59). Such process does not represent merely a marker of inflammation but plays a potentially relevant role in the pathogenesis of CSU as many activated coagulation factors (*e.g.*, FVIIa, FXa and FIIa) are able to activate mast cell via protease activated receptors, and C5a generated by the thrombin-dependent pathway (60) participates in mast cell degranulation via the C5aR. The activation of the coagulation cascade parallels the disease activity (61, 62) and stops suddenly and dramatically as soon as the disease goes into remission (*e.g.*, after the start of successful omalizumab) (63-65).

### Type IIb autoimmunity: not only mast cells and basophils

In CSU eosinophils, which may play a relevant pathogenic role via the expression of TF, may be activated through IgG autoantibodies to the membrane low-affinity IgE receptor FcεRII.

**Figure 1** - Some milestones in the understanding of the pathogenesis of CSU leading to the identification of different endotypes.



Such autoantibodies have been detected in about 65% of patients with CSU (66). The activation of eosinophils leads to the release of major basic protein (MBP) which is able to degranulate mast cells via the Mas-related G protein-coupled receptor X2 (MRGPRX2) which is upregulated in CSU patients (67-69). Further, eosinophils are a major source of vascular endothelial growth factor (VEGF), the most active vasodilator substance known (70) which is also hyper-expressed in CSU patients.

### Beyond autoimmunity and autoallergy

There is evidence that in CSU, mechanisms leading to histamine release other than autoantibodies are present and active. In one study, sera from CSU patients were able to degranulate HMC-1, a mast cell line missing the high affinity IgE receptor, as well as LAD-2 (a mast cell line showing the FcεRI receptor) irrespective of a positive or negative autologous serum skin test (71). In a subsequent study, both whole serum and serum fractionated at 100, 50, and 30 kDa, including fractions < 30 kDa, from CSU patients were able to activate LAD2 mast cells significantly more than the corresponding fractions from normal control sera (72). Although these low-molecular weight histamine-releasing factors have not been further characterized, the recent observations about the potential relevance of the MRGPRX2 receptor (67), suggest that neuropeptides, such as substance P, and eosinophil-derived proteins, including major basic protein and eosinophil peroxidase, may play a role in mast cell activation and contribute to CSU pathogenesis (69,

73). These findings confirm the pioneering observations by Grattan and co-workers who first hypothesized the role played by low molecular weight histamine releasing factors in CSU (74). A summary of the current knowledge about the pathogenesis of CSU is shown in **figure 1**, and a chronological list of the milestones in urticaria research is shown in **figure 2**.

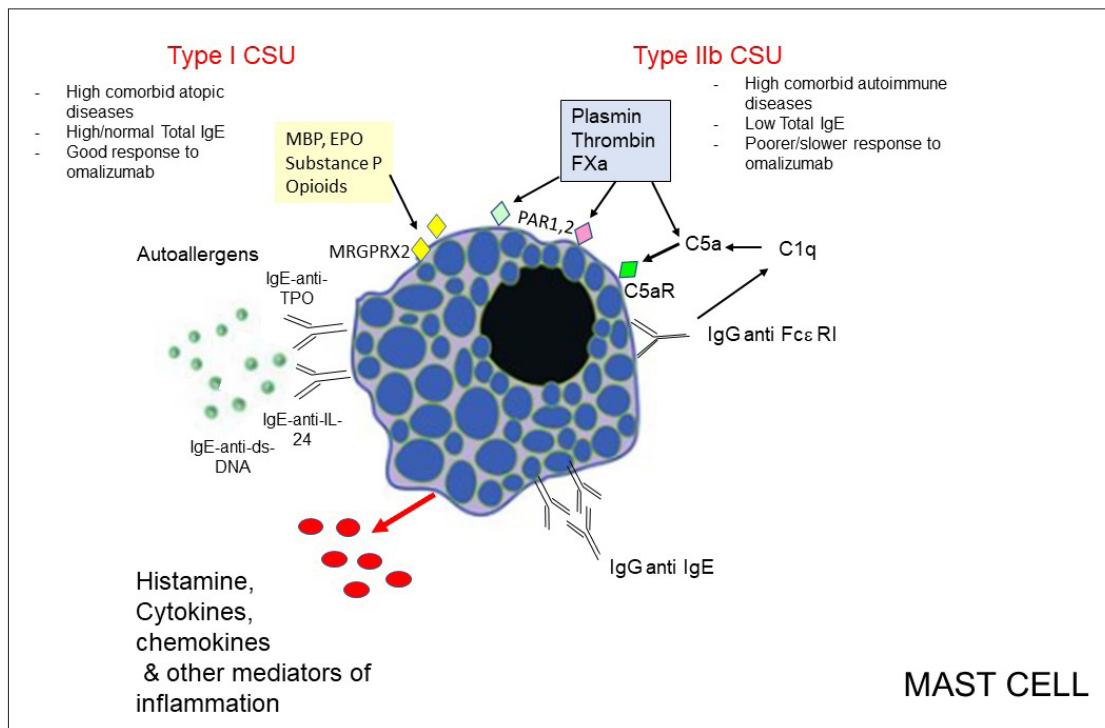
### Are parasitoses and malignancies potential causes of CSU?

Before the identification of the autoimmune and autoallergic pathogenic mechanisms underlying CSU, much research has been devoted to seek for possible systemic causes of the disease, in particular parasitic diseases and malignancies. In 2016 a systematic review of internal parasitic infections in chronic urticaria (75) concluded that, albeit these were more frequently diagnosed in CSU patients than in the general population (maybe because they were more actively sought for), they were an uncommon underlying cause of the disease. The association of malignancies with CSU is extremely rare, and when such association occurs urticaria resolves with the cure of the neoplasm (76).

### Conclusions

Although there are still several gaps to fill before we can claim that the CSU enigma has been solved, our knowledge about this disease has much improved and is still evolving. Chronic spontaneous urticaria is probably not a single, well-defined disease

**Figure 2** - A summary of current knowledge of the different endotypes in chronic spontaneous urticaria. The two endotypes may co-exist.



but rather an umbrella term referring to a clinical phenotype under which several different endotypes probably exist. A large number of novel therapies for antihistamine- and cyclosporin-refractory CSU patients are being studied. Hopefully, some of them will allow us to personalize the treatment for each single patient in the future.

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None.

### Contributions

RA: conceptualization, writing – original draft, writing – review & editing. AT: review & editing.

### Conflict of interests

The authors declare that they have no conflict of interests.

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