The Role of Infection and Autoimmunity in Urticaria and Angioedema as a Common Entity

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Disclosure: The author has declared no conflicts of interest.

Received: 06.06.20

Accepted: 15.02.21

Keywords: Angioedema, COVID-19, *Helicobacter pylori*, herpes, urticaria.

Citation: EMJ Allergy Immunol. 2021;6[1]:79–85.

Abstract

Chronic spontaneous urticaria with angioedema is prevalent, affecting approximately 1% of the general population, and has a significant impact on quality of life, according to epidemiological data. This article aims to broaden the view on the mechanisms of urticaria and the role of infection in the current environment. It is not easy to identify the cause of urticaria but appropriate steps to treat an underlying infection can, in some cases, improve the symptoms of urticaria and angioedema, reduce severity and duration, or lead to remission.

Although chronic spontaneous urticaria with angioedema is a multifactorial condition involving inflammation, autoimmunity, and coagulation, IgE-mediated autoimmunity, or autoallergy, is thought to play a major role. Every year, more is learnt about the role of cells releasing mediators, underlying autoimmune processes that lead to the development of mast cell activation and urticaria.

It has become increasingly clear that mast cell roles in immune system responses are not limited to an allergic role; they are key players in protective immune responses, both innate and adaptive, to various pathogens and in defence of some infections.

Several guidelines, consensus papers, and practice parameters have been developed for the management of chronic urticaria. The Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GA^{2}LEN), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO) produce a guideline, which is revised every 4 years by a global panel of experts in the field. Infections may be a cause, aggravating factor, or unassociated bystander in chronic urticaria.

The author looked at evidence, using a keyword search, for the role of viral and bacterial infections in acute, acute recurrent, and chronic urticaria and angioedema, including COVID-19, herpes, viral hepatitis, and *Helicobacter pylori*.

INTRODUCTION

Urticaria is a highly prevalent, mast-cell-driven skin disorder with recurrence of transient wheals that can occur with or without angioedema.[1,2] Urticaria affects between 15% and 25% of the population at some point during their lifetimes.[3] Urticaria is characterised by the development

of wheals, angioedema, or both. Chronic urticaria is defined by recurrently appearing signs and symptoms for >6 weeks. The disease activity of all chronic urticaria subtypes can markedly change over time and differ between individual patients.[4]

The condition tends to be more common in adults than in children and in females than in males, with peak occurrence in the third to fifth decades of life. This condition is marked by the onset of pruritic wheals, which represent well-circumscribed areas of non-pitting oedema with blanched centres and raised borders that involve only the superficial portions of the dermis and are seen in conjunction with surrounding erythema of the skin.[5]

The discussion of the role of infectious diseases in urticaria has been continuing for more than 100 years. It is evident that the eradication of the infection could lead to the resolution of urticaria; however, a causal relationship with underlying or precipitating infection is difficult to establish.[6]

Different studies have reported that multiple infections range from 37% to 58% among patients diagnosed with urticaria.[7] There are several theories for the pathogenesis of the potential autoimmune nature of this condition, associated with approximately 50% of cases.[8] It is understood that the underlying mechanism of urticaria is caused by activation of mast cells and basophils, which release pro-inflammatory mediators that result in increased permeability of blood vessels and irritation of nerve endings, leading to swelling and pruritus.[9]

Current research in chronic spontaneous urticaria (CSU) targets the role of cells and released mediators that lead to the development of urticaria through mast cell activation, with a focus on the underlying autoimmune processes.[10] Although CSU is a multifactorial condition involving autoimmunity, coagulation, and inflammation,[11] IgE-mediated autoimmunity, or autoallergy, is thought to play a major role.[12]

Histamine release likely occurs through cross-linking receptors by IgG-specific and specific auto-immune IgE autoantibodies derived against antigens, on mast cells and basophils.[13]

IgG anti-FcεR1α induces histamine release irrespective of the degree of IgE sensitisation of the basophils. As proof of concept, histamine release was effectively neutralised in a concentration-dependent manner by pre-incubating donor basophils with a soluble fragment of FcεR1α prior to the addition of purified IgG from sera of patients diagnosed with CSU.[12] It was shown that circulating IgG antibodies against IgE and the high-affinity IgE receptor FcεR1 likely played a role.[14] Approximately 40% of patients have circulating antibodies to one of these targets, with a higher frequency of positivity in patients who are autologous serum skin test positive.[15]

Anti-FcεR1 antibodies are thought to be the more common of the two. FcεR1 is found on the surface of both dermal mast cells and basophils, and autoantibodies to this receptor can provoke chronic stimulation and degranulation of these cells in an IgE-independent fashion.[16] In contrast, IgG anti-IgE antibodies may bind to and cross-link receptor-bound IgE on the surface of mast cells and basophils, leading to activation and degranulation of these cells.

Protein microarray analysis showed that patients diagnosed with CSU have higher IgE levels than healthy individuals, and IgE are directed mainly to thyroid antigens and double-stranded DNA.[12] Cholinergic urticaria is a frequent form of inducible urticaria, characterised by small, itchy wheals induced by physical activity or passive warming. The underlying causes are not completely understood. Several recent studies have provided evidence that IgE-mediated mast cell activation is of major importance in the pathogenesis.[13]

In approximately 10% of patients, urticaria is linked to rare factors: allergic urticaria,[17] salt-dependent aquagenic urticaria that has been reported in adults and two cases have now been reported in children.[18] Twenty five reports of chronic urticaria and malignancy raised the possibility that chronic urticaria and malignancies are linked in some patients.[15] Recently, two additional cases of cancer and chronic urticaria have also been reported, with resolution of urticaria once the tumour was removed.[19,20]

Exposure to phthalates (substances used primarily to soften polyvinyl chloride) was shown to increase the risk of acute urticaria in children.[21] Nearly all of the numerous studies reporting

evidence for infectious agents triggering acute or recurrent acute urticaria were retrospective observational studies without appropriate controls or were case reports.[22] There were reports of *Mycoplasma pneumoniae* infection in 32% of 65 children with acute urticaria.[23] There were observations of urticaria symptoms after influenza vaccination.[24] Upper respiratory or digestive symptoms are common with urticaria associated with infections.[25,26]

Other reports focused on an association between acute urticaria and streptococcal infection,[30] hepatitis A[28] and B viruses,[30] *parvovirus B19*, *cytomegalovirus* (CMV),[29] *Coxsackie A9* virus,[31], *enterovirus*, influenza A,[24] and parainfluenza viruses. Viral infection can be a potential trigger and sometimes the main aetiologic agent in causing acute or chronic urticaria.[32]

Several hypotheses exist that hepatitis B or C infection may enhance IgE-induced mediator release from mast cells and basophils.[33]

Protein factor V, which is produced during viral hepatitis, can activate human basophils and skin mast cells to release histamine and other mediators.[34] Factor V protein acts as an endogenous super-antigen by interacting with the VH3 domain of IgE to induce the activation of mast cells.[35]

As only <5% and 2% of patients diagnosed with CSU have hepatitis B and C, respectively, the rates of infection do not appear to be increased in patients diagnosed with CSU, suggesting that viral hepatitis and CSU are not usually linked.[36]

Acute infection with viral pathogens in the *Herpesviridae* family can trigger acute urticaria, and reactivation of *Herpesviridae* is associated with cutaneous urticarial-like syndromes. Reactivation of latent *Herpesviridae* has not been studied systematically in chronic idiopathic urticaria and CSU.[37] CSU is an inflammatory disorder with autoimmune features (termed chronic viral urticaria) based on serology, consistent with the hypothesis that reactivation of a latent human *herpesvirus* (HHV) or viruses may play a role in CSU.[37]

Patients diagnosed with CSU also exhibited serological evidence of increased immune response to HHV-4 (*Epstein–Barr* virus) but not all patients diagnosed with CSU were infected with Epstein–Barr virus. These observations, combined with case reports of CSU response to antiviral therapy, suggest that HHV-6, possibly interacting with HHV-4 in cutaneous tissues, is a candidate for further prospective study as a co-factor in CSU.[37]

In the beginning of the COVID-19 outbreak in Wuhan, urticaria was self-reported among community-acquired cases in 1.4% of patients, with an approximately 1:1 ratio of male (50.7%) and female patients, with an overall median age of 57.0 years.[38] From a series of 88 patients, 20% developed cutaneous manifestations including erythematous rash, widespread urticaria, and chickenpox-like vesicles.[39] In a later publication, cutaneous manifestations of COVID-19 infection included a papulovesicular rash (34.7%; 25/72), and urticaria (9.7%; 7/72).[40]

Many bacterial infections have been associated with urticaria manifestation, such as *Helicobacter pylori*, *Streptococcus*, *Staphylococcus*, *Mycoplasma pneumoniae, Salmonella*, *Brucella*, *Mycobacterium leprae, Borrelia*, *Chlamydia pneumoniae*, and *Yersinia enterocolitica.* In some cases, the skin manifestations, described as urticaria, could be caused by the presence of the microorganism in the skin, the action of their toxins, or complement activation mediated by circulating immune complexes. Although only a weak association with urticaria of unclear pathogenesis exists, clinicians should consider these bacterial agents in the work-up of the patients diagnosed with urticaria. The eradication of the infection could, in fact, lead to the resolution of urticaria.[6]

Seropositivity of anti-*H. pylori* antibodies was higher in the urticaria-diagnosed patients than in control groups. *H. pylori* is a spiral-shaped micro-aerophilic Gram-negative bacterium that colonises the gastric mucosa and induces a strong inflammatory response with release of various bacterial and host-dependent cytotoxic substances.[41] The existence of a correlation between *H. pylori* and urticaria may help clinicians to find more effective methods to treat patients diagnosed with chronic urticaria.[32]

H. pylori is a risk factor for developing chronic urticaria; therefore, stool test for *H. Pylori* antigen is recommended.[42] Meta analysis showed that *H. pylori* might be associated with the occurrence

and persistence of CSU. The effectiveness of *H. pylori* eradication therapy in suppressing CSU symptoms was significant. Interestingly, it was found that resolution of CSU was not associated with successful eradication of *H. pylori* infection. Patients diagnosed with urticaria who had undergone antibiotic therapy for *H. pylori* eradication showed significantly higher CSU remission, with or without *H. pylori* eradication.[43]

Autoimmune mechanisms are contributing to the pathogenesis of chronic urticaria; different pathogenic autoantibodies, causing a release of histamine after reaction with IgE epitopes, or with the α-chain of Fc epsilon RI receptors, are considered.[44] Lesions can be as small as a few millimetres in diameter but can coalesce to form wheals as large as several centimetres wide. They often remit within 24 hours from time of onset. Urticaria may be accompanied by the presence of angioedema, which is a similar process that occurs at submucosal surfaces of the upper respiratory and gastrointestinal tracts and deeper layers of the skin including subcutaneous tissue.[45]

Urticaria is mainly classified based on clinical criteria: acute and chronic urticaria. Chronic urticaria comprises both CSU and chronic inducible urticaria that includes physical and non-physical urticarias.[46] CSU is a common and complex condition lasting for more than six weeks, and occurs without an identifiable causative factor. This skin disease in a sub-group of patients is related to autoreactive IgE, but the nature of this autoreactive IgE is still poorly characterised.

Formerly referred to as chronic idiopathic urticaria, CSU refers to recurrent urticaria lasting more than 6 weeks, that occurs in the absence of an identifiable trigger. Urticaria that are incited by a well-defined eliciting factor (e.g., pressure, temperature, vibration) are referred to as inducible urticaria and will not be further discussed in this review. Prevalence of chronic urticaria is estimated to be anywhere from 0.5–5% in the general population but is not truly known.[47] Recent guidelines now include isolated idiopathic angioedema within the definition of CSU provided that other causes of angioedema, particularly those that are bradykinin mediated, have been excluded.[48] Epidemiological data indicate that CSU in the general population is prevalent in approximately 1%[49] and has a significant impact on quality of life.[50]

CLINICAL APPROACHES

Diagnosis and Treatment Approaches in Chronic Spontaneous Urticaria Differ in Various Parts of the World

There are no currently available biomarkers that can be used for the evaluation and management of patients diagnosed with CSU. Potential biomarkers of CSU severity and/or duration include basophil numbers and susceptibility to activation, inflammatory markers, markers of activation of the extrinsic coagulation pathway, immunoglobulin E, and vitamin D. Although the described markers are promising, further studies on representative and well-characterised patient populations are needed to determine the value of these clinical and biological markers for predicting the severity and course of disease in patients with CSU.[51]

An 'urticaria diary' can be very helpful for assessment. It should be used over several weeks to document information on the frequency and intensity of symptoms (e.g., wheals, itch, swelling, and systemic symptoms), possible relevance with physical factors, food intake and other activities (e.g., physical or emotional stress), and patient's medication.

The Urticaria Activity Score (UAS) is based on the evaluation of numbers of wheals and the intensity of itching using a 0–3-point scale. It is calculated as the daily sum of the wheal and itch score, with a maximum score of six points per day and 42 points per week (for the UAS 7).

There are three possible underlying causes of CSU: infections, food intolerance, and auto-reactivity.[52] Bacterial infections, as well as viral, fungal, or parasitic infections can be a cause of CSU. The current guidelines recommend differential blood count analyses, determination of blood sedimentation rate and C-reactive protein, together with a focused patient history for discovering potentially relevant infections.[2]

Testing for *H. pylori* (stool, breath test, or demonstration of antigen/antibodies) are recommended.

Higher levels of C-reactive protein (CRP) were associated with autologous serum skin test positivity, arterial hypertension, urticaria activity, quality of life impairment, inflammatory and coagulation markers, and poor response to antihistamines. Elevated levels of the sensitive inflammatory biomarker CRP are suggested for diagnosis and disease activity of CSU.[53] Recent findings have demonstrated that IgE anti-thyroid antibodies are present at higher frequency and amounts in patients diagnosed with CSU and have greater potential to induce thyroid autoantibody-mediated skin reactions in these subjects versus healthy controls.[54]

A systematic review that assessed the relationship between vitamin D and CSU showed statistically significant lower serum vitamin D levels in CSU-diagnosed patients compared to controls, and disease improvement after high-dose vitamin D supplementation. Vitamin D deficiency was reported more commonly for patients diagnosed with CSU (34.3–89.7%) than in controls (0.0–68.9%).[55] When history indicates a possible inducible pattern, physical skin tests (e.g., cold, heat, ultraviolet light, and pressure) as well as exercise tests should also be performed in order to verify or rule out inducible urticarias. To perform these tests antihistamines must be discontinued for at least 2–3 days.

If high or low temperature contact urticaria is suspected, skin testing with TempTest® (MOXIE GmbH, Berlin, Germany) can be used as a diagnostic tool as well as to monitor responses to treatment. The provocation testing is performed for 5 min with a temperature 4–45° on the volar forearm. The provocation time and temperature can be adapted individually. If a palpable, clearly visible wheal and flare-type skin reaction occurs, the test reaction is rated positive. Eosinopenia in patients diagnosed with CSU is associated with Type IIb autoimmunity (markers include autoantibodies, basophil tests, and/or autologous serum skin test), high disease activity, and poor response to treatment. Eosinophils should be explored as biomarkers and investigated for their contribution to the pathogenesis of CSU.

Subjects with IgE autoantibody-mediated CSU appear to have a faster onset of improvement in response to omalizumab than those with IgG-mediated disease, due to the unique mechanisms by which this drug sequentially affects IgE levels and FcεR1 status.

On the contrary, subjects who display a slow response to omalizumab are thought to have IgG antibodies against FcεRI since down-regulation of this receptor occurs only after free IgE is first complexed by the drug. The authors validated this hypothesis by demonstrating a high correlation between length of time to the onset of omalizumab efficacy and positive basophil histamine release activity, with the latter predicting slower response times to treatment.[56]

A recent study in 49 Caucasian patients diagnosed with CSU found elevated levels of specific IgE against a mix of *Staphylococcus aureus* enterotoxins in 51% of patients compared to 33% in healthy controls.[57] Total serum IgE levels and CSU disease activity were correlated with *Staphylococcus* enterotoxin B IgE levels. These results suggest a role of *S. aureus* enterotoxin IgE antibodies in the pathogenesis of CSU, in keeping with the current hypothesis of autoallergy being important in some patients.

In cholinergic urticaria that is actively (e.g., due to exercise) or passively (e.g., having a hot bath) induced, increases of the body temperature result in the appearance of itching and formation of wheals. Typically, the wheals are tiny, short-lived, and accompanied by a pronounced flare reaction, which is often localised on the limbs and trunk.[58] This form of urticaria should be differentiated from exercise-induced urticaria/anaphylaxis, in which exercise but not passive warming provokes symptoms (cutaneous and more frequently than in cholinergic urticaria, systemic symptoms). In the differential diagnosis, attention should be given to food or drug-dependent exercise-induced anaphylaxis.

CONCLUSION

The understanding, knowledge, and management of urticaria and angioedema are rapidly increasing. It was noted that in some patients, treatment of the underlying pathology led to clinical improvement. Further research is required to gain understanding of the mechanisms of interaction between infection and urticaria and angioedema. Interdisciplinary co-operation with dentists and ear, nose, and throat specialists, and X-ray and serological analysis for streptococcal (anti-streptolysin) or staphylococcal infection should be performed to identify bacterial infections

of the nasopharynx, e.g., recurrent sinusitis or tonsillitis.[51,59]

Data obtained indicated viral infection as a potential trigger and sometimes as the main aetiologic agent in causing acute or chronic urticaria. In every case, urticarial manifestation cleared up after either healing or controlling of the viral infection. However, prospective studies and well-structured research are needed to better clarify the role of viruses in the pathogenesis of urticaria and their relative prevalence.[60]

The author can hypothesise that the underlying lasting immune response to an infection, rather than infection itself, is the causative factor for persistence of urticaria, alongside autoimmune factors. Antibodies and co-factors acting together reduce the threshold of reactivity leading to symptoms.

Many questions and unmet needs remain to be addressed, such as the development of routine diagnostic tests for autoimmune urticaria and angioedema; the global dissemination and consistent use of tools to assess disease activity, impact, and control; and the development of more effective and well-tolerated long-term treatments for all forms of urticaria and angioedema.

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