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Chronic Urticaria and Angioedema: Review Article

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ABSTRACT

Background: Chronic urticaria (CU) and angioedema are common characterized by repeated wheals, pruritus, and recurrent deep tissue swelling lasting for more than six weeks. CU has an impact on patients with quality of life and is hard to diagnose and manage. The condition is usually classified as chronic spontaneous urticaria (CSU), for which there is no underlying cause, and chronic inducible urticaria, which occurs following exposure to specific stimuli such as pressure, cold, or heat. Angioedema may occur in isolation or with urticaria and commonly involves the face, lips, tongue, and airway and may prove fatal under rare conditions.

Objective: This article throws a deep overview on chronic urticaria and angioedema, their epidemiology, pathogenesis, clinical classification, diagnostic strategy, and current therapeutic strategies.

Methods: From 2005 to June 2025, a thorough search was carried out in PubMed, Google Scholar, and Science Direct using the following keywords: Angioedema, Chronic urticarial, Histamine, Mast cells, Omalizumab. Only the most recent or comprehensive study was considered. Oral presentations, dissertations, conference abstracts, and unpublished papers are a few examples of works that weren't considered important scientific study. Documents published in languages other than English were ignored as a result of lack of translation resources.

Conclusion: Although the exact pathogenesis remains unclear, autoimmune features, mast cell activation, and histamine release are all crucial considerations. The diagnosis is clinical with support from detailed history, physical examination, and selective laboratory evaluation. Non-sedating H1-antihistamines form the first-line of treatment with dose escalation as needed. Refractory cases may require omalizumab, cyclosporine, or other immunomodulators. Effective management relies on correct diagnosis, identification of associated causes or comorbidities, and stepwise treatment in accordance with international guidelines. Unraveling of disease mechanisms and therapeutic approaches will increasingly develop through research.

Keywords: Angioedema, Chronic urticarial, Histamine, Mast cells, Omalizumab.

INTRODUCTION

Chronic urticaria (CU) and angioedema are disabling dermatoses with a significant effect on quality of life. Defined by the development of wheals, angioedema, or both lasting longer than six weeks, chronic urticaria affects approximately 0.5–1% of the population at any given time [(1).] Chronic urticaria is an acute emergence of pruritic, erythematous swellings of the skin that is not uncommonly occur without an apparent external stimulus. Angioedema, when occurring concomitantly or independently, involves more profound subcutaneous and dermal tissue, with subsequent transient swelling of the lips, eyelids, and genitals. The chronicity and unpredictability of such appearance render it a serious diagnostic and therapeutic challenge [(2)].

The etiology of chronic urticaria and angioedema is multifactorial and in the majority of instances is idiopathic. Autoimmunity, infections, pseudoallergens, and systemic diseases are commonly implicated in the pathogenesis of chronic urticaria. Angioedema, when associated with urticaria, would normally have identical underlying etiopathogenic mechanisms but may also be caused by other mechanisms, i.e., bradykinin-mediated mechanisms in hereditary or acquired angioedema [(3)]. The establishment of histaminergic vs. non-histaminergic etiology is of the utmost significance because prognostics and therapeutic guidelines are different accordingly. The advancements in the field of immunopathology have recognized autoimmune subtypes of CU, such as chronic spontaneous urticaria (CSU) with autoantibodies to the high-affinity IgE receptor or IgE itself [(4)].

Treatment of angioedema and chronic urticaria has been revolutionized in the last decade with international agreement and evidence-based practice guidelines. First-line treatment of choice is typically second-generation non-sedative H1-antihistamines, with dose escalation in refractory patients [(5)]. In refractory patients to treatment, omalizumab, an anti-IgE monoclonal antibody, has been extremely effective. Leukotriene receptor antagonists, cyclosporine, and experimental biologics are some of the other treatment modalities. There is a subset of patients who are refractory to all of these treatments, mandating the development of individualized and multi- disciplinary treatment plans [(6)].

This review will give an in-depth overview of chronic urticaria and angioedema, their epidemiology, pathogenesis, clinical classification, diagnostic strategy, and current therapeutic strategies. Emphasis were given

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to the latest advances concerning immunological mechanisms and novel treatments. Specific attention will be given to at-risk groups, such as children and pregnant women. By compiling the available evidence, the article seeks to help clinicians diagnose and treat these complex conditions successfully.

PREVALENCE OF URTICARIA AND ANGIOEDEMA GLOBALLY AND IN EGYPT

Urticaria and angioedema are prevalent dermatologic conditions that cut across all ages globally. Global urticaria prevalence depends on the population being studied, the study method, and the type of subtype measured. It is estimated that a total of 20% of the population at large will have at least one case of urticaria throughout their lives [(7)]. Acute urticaria is more common, especially in young adults and children, and tends to be self-limiting. Chronic urticaria (CU) affects approximately 0.5% to 1% of the population at any given time. Of these, the most frequent subtype of chronic urticaria is chronic spontaneous urticaria, with chronic inducible forms occurring less commonly but often being underdiagnosed due to symptom overlap as well as diagnostic difficulty [(8)].

The prevalence of angioedema is more difficult to establish due to multifactorial etiologies and frequent co-occurrence with urticaria. If expressed relative to histamine-mediated conditions, angioedema occurs in approximately 40% to 50% of patients with chronic urticaria [(9)]. However, non-histaminergic angioedema, such as hereditary angioedema (HAE) or angiotensin-converting enzyme (ACE) inhibitor-associated angioedema, is significantly less frequent. HAE, a genetic disorder that is uncommon, is found in an estimated 1 in 50,000 individuals globally, although geographic precise estimates vary [(10)].

In Egypt and other North African and Middle Eastern countries, urticaria and angioedema epidemiological data are still rare but have been more and more described in hospital-based and community-based studies. Egyptian studies described chronic urticaria to be slightly higher than the international prevalence in several studies, which may be affected by environmental causes, vast prevalence of infections and parasitic disorders, and increased prevalence of autoimmune disease [(11)]. Some hospital-based studies from allergy and dermatology clinics suggest that urticaria forms part of 3–5% of outpatient dermatological visits. Food allergies and infections are a more common cause of acute urticaria, especially in children, whereas chronic urticaria is more prevalent in women of the third to fifth decades of their lives [(12)].

RISK AND TRIGGER FACTORS OF CHRONIC URTICARIA

Chronic urticaria is a multifactorial disorder with numerous causes. Both its cause and maintenance involve a combination of intrinsic risk factors and extrinsic inducing stimuli. Although in the majority of cases the etiology is idiopathic, evidence is mounting for a variety of causative risk factors that predispose patients to chronic urticaria, and clinically identifiable triggers that can precipitate or aggravate the illness [(13)].

Female sexuality is also one of the strongest-established risk factors for chronic urticaria, with women being afflicted roughly twice as often as men. This gender distinction is almost certainly because of the influence of hormones and the lower prevalence of autoimmune illnesses in men. A second risk factor is age, the condition occurring more commonly in adults, particularly in the age group 20-50 years [(14)]. Genetic predisposition may be a factor in family history of atopic or autoimmune conditions. Further, patients who experience stress, anxiety, or depression have been found to be at high risk for developing or maintaining recurrent CU symptoms, suggesting a role for neuroimmune mechanisms of disease pathogenesis [(15)].

Trypanosomatid parasites, which infect and reside within cells, have historically been considered both pathogenic and innocent. Autoantibodies to the high-affinity IgE receptor (FcεRI) of mast cells or to IgE itself have been detected in a high percentage of patients [(16)]. They lead to chronic activation of basophil and mast cells, with resultant chronic release of histamine and other proinflammatory mediators. Chronic urticaria is also more common in those with other autoimmune diseases such as autoimmune thyroiditis, systemic lupus erythematosus, and type 1 diabetes, once more indicating an autoimmune origin in the majority of cases [(17)].

Aside from the risk factors mentioned above, several precipitating or exacerbating factors may induce or trigger attacks of urticaria in at-risk individuals. Physical stimuli are some of the most frequent causes in chronic inducible urticaria. Pressure (e.g., pressure urticaria with a time delay), cold, heat, sun exposure (solar urticaria), vibration, and water immersion are additional examples [(18)]. Infections, particularly viral and parasitic infections, also have been found to be involved in the provocation or aggravation of CU, particularly in endemic regions. NSAIDs are known triggers in the majority of patients and may exacerbate urticaria, perhaps due to an effect on prostaglandin pathways and mast cell activation [(19)].

Food additives, preservatives, and pseudoallergens i.e., artificial colors, benzoates, and certain naturally occurring food substances may also cause or maintain symptoms of chronic urticaria, although true food allergy is uncommon in adult CU. Environmental allergens, thermal changes, and even hormonal change accompanying menstrual cycles may also act as

precipitating factors. In some patients, H. pylori infection or other gastrointestinal pathology have been associated with chronic urticaria, and eradication treatment can lead to selected improvement [20].

CLASSIFICATION

Urticaria and angioedema can be acute or chronic and spontaneous or inducible, depending upon the etiology. On the basis of duration, etiology, and pathophysiology, urticaria and angioedema can be classified. Primary classification is on the basis of duration: Acute (duration of< 6 weeks) and chronic (duration of ≥ 6 weeks). Chronic urticaria is classified further into chronic spontaneous urticaria (CSU), with no detectable external cause, and chronic inducible urticaria, which is induced by specific physical or environmental stimuli such as cold, heat, pressure, sun, vibration, or water [9].

Angioedema is also classified into histaminergic angioedema, often accompanied by urticaria and responsive to antihistamines, and bradykinin-mediated angioedema, including hereditary angioedema (HAE) and ACE inhibitor-induced angioedema, typically without pruritus and urticaria and not responsive to antihistamines or corticosteroids [21].

SYMPTOMS AND SIGNS

The typical symptom of urticaria is intense pruritus with raised, erythematous, and transient wheals with central pallor. The lesions may be irregular in size and shape, sometimes clustered or diffusely spreading over the body, and usually resolve within 24 hours without leaving any residual lesions. In chronic disorders, the wheals recur daily or intermittently. Angioedema is deeper swelling of the dermis and subcutaneous tissue, which may be painful or burning rather than pruritic. It has a propensity to involve loose connective tissue areas, such as the periorbital and perioral regions, extremities, gastrointestinal tract, and genitals. Involvement of the tongue, larynx, or airway can cause respiratory compromise and is an emergency [22].

STAGES

Although urticaria and angioedema are not formally described in traditional "stages" such as chronic disease or cancer, their clinical course may be considered in onset, peak, and resolution phases.

- **Initiation (Triggering Phase):** In this first phase, exposure to allergens (foods, insect stings, or drugs), physical stimuli, infections, or internal autoimmune mechanisms activates mast cells and basophils to secrete histamine and other mediators.
- **Active (Symptomatic Phase):** Marked by the acute onset of wheals or edema. Symptoms are most severe, with severe pruritus in urticaria or edema and pain in angioedema. Duration is indefinite but typically short-term in acute and chronic or remitting in chronic.
- **Resolution (Recovery Phase):** As there is no ongoing exposure or underlying condition, the skin lesions and swelling improve by themselves. Urticarial lesions resolve within 24 hours, and it takes 24 to 72 hours for angioedema to resolve completely. In chronic urticaria or hereditary angioedema, this is a temporary phase because the symptoms have a tendency to recur periodically [23].

Understanding the classification, symptoms, and natural history of urticaria and angioedema is important in making the correct diagnosis, determining potential causes, and guiding appropriate treatment strategies in preventing recurrence and managing complications [9].

DIAGNOSIS

In most cases of chronic urticaria, complete laboratory investigations are not generally required, especially when there is no suggestion of systemic disease. However, a limited number of investigations can be useful in the exclusion of underlying causes or associated conditions. These may include a complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), thyroid function tests, and anti-thyroid antibodies. Additional tests such as antinuclear antibodies (ANA), serum tryptase, or stool for parasites may be requested based on the clinical context [24].

In isolated angioedema, especially recurrent or severe, additional evaluation is needed to determine whether it is histaminergic or bradykinin-mediated. Histaminergic angioedema is treatable with antihistamines and may be a component of CU, while bradykinin-mediated forms such as HAE or ACE inhibitor-induced angioedema are not. Investigation of suspected HAE includes C4 complement level, C1 esterase inhibitor (C1-INH) level and activity, and in some cases, genetic investigation. Normal C4 level during an acute attack makes HAE less likely, while low C4 with low or dysfunctional C1-INH confirms the diagnosis [25].

TREATMENT

The management of CU and angioedema is challenging with the goal of symptom control, improving quality of life, and seeking underlying or exacerbating factors. As both are distressing and can be recurrent, stepwise and individualized treatment is required. Urticaria and angioedema often co-occur but can have varying therapeutic responses according to the underlying mechanisms namely, whether they are histamine-mediated or bradykinin-mediated [26].

Treatment starts with the recognition and avoidance of offending stimuli. These may include NSAIDs, foods or additives, physical stimuli, and infections. A good history is needed to identify potential exacerbating agents. If no apparent trigger is found, the condition is termed CSU, and treatment is primarily pharmacologic symptom management [8].

First-line management is based on the use of non-sedating second-generation H1-antihistamines. These drugs, including cetirizine, loratadine, fexofenadine, and desloratadine, are the preferred drugs due to their favorable safety profile and minimal central nervous system effects. In the event that the standard doses are not effective in controlling symptoms, guidelines are to quadruple the dose. Studies have established that these higher doses are effective in the majority of patients without a notable risk of enhancing adverse effects [27].

If high-dose antihistamines are insufficient, third-line treatment consists of the addition of omalizumab, a monoclonal anti-IgE antibody. Omalizumab is approved for antihistamine-resistant chronic spontaneous urticaria and showed excellent efficacy for the alleviation of both wheals and angioedema, often leading to the virtual abolition of symptoms. It is administered subcutaneously, usually every 4 weeks, and is generally well-tolerated [28].

For non-responders to omalizumab or those who have more severe disease, immunosuppressive medications such as cyclosporine A can be employed. Cyclosporine suppresses the activation of T cells and mast cell mediator release but must be closely monitored due to its nephrotoxicity and other adverse effects. Less frequently utilized medications include leukotriene receptor antagonists, dapsone, or systemic corticosteroids, but the latter is not recommended for chronic use due to its unfavorable safety profile [29].

In the management of angioedema, it differs based on whether it is histamine-mediated or bradykinin-mediated. Histamine-mediated angioedema, which often appears in association with urticaria, typically responds to the same therapies—antihistamines, omalizumab, or corticosteroids for acute flare-ups. Nevertheless, bradykinin-mediated angioedema, such as HAE or ACE inhibitor-induced angioedema, is not responsive to antihistamines or corticosteroids. Therapy in these cases involves targeted therapies such as C1 esterase inhibitor replacement therapy, bradykinin receptor antagonists and plasma kallikrein inhibitors. In HAE, long-term prophylaxis with agents such as lanadelumab or attenuated androgens may be indicated in some patients [30].

Reassurance and patient education are also important in every case. Educate patients about the typically benign nature of chronic urticaria, the importance of compliance with therapy, as well as the possible precipitants to avoid. The use of validated measures such as the Urticaria Activity Score (UAS7) and the Angioedema Activity Score (AAS) can also give a method of tracking disease activity and response to treatment over time [31].

CONCLUSION

Chronic urticaria and angioedema are complex, frequently distressing conditions with high quality-of-life impact on patients. Despite their prevalence, diagnosis is largely clinical and frequently delayed due to the wide range of underlying conditions and the absence of definitive biomarkers in most instances. Thorough history, thorough physical examination, and selective laboratory investigations are also important in distinguishing between chronic spontaneous and chronic inducible urticaria and distinguishing between histaminergic and bradykinin-mediated angioedema.
Accurate diagnosis is not only important for the institution of proper treatment but also for the prevention of unnecessary tests and procedures. Despite the cornerstone of treatment being second- generation H1-antihistamines, treatment-resistant cases require escalation to medications such as omalizumab or cyclosporine, highlighting the need for individualized stepwise treatment approaches according to international guidelines. Continued research into the immunopathogenesis and molecular mechanisms of chronic urticaria and angioedema will foster ever more targeted, effective therapies. Lastly, raising clinician awareness and patient education remains the cornerstone of early diagnosis, optimized treatment, and an improved long-term prognosis.

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