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Chronic Urticaria: Pathophysiology, Diagnosis, and Advances in Targeted Therapies

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Abstract

Chronic urticaria (CU) is a skin disorder characterized by recurrent wheals, angioedema, or both, persisting for more than six weeks. It can significantly impair quality of life due to persistent itching, discomfort, and the unpredictable nature of flare-ups. While the exact etiology remains unclear in many cases, autoimmune mechanisms, histamine release from mast cells, and environmental triggers play a key role in disease manifestation. Diagnosis relies primarily on clinical history and exclusion of underlying causes through laboratory and imaging investigations. Traditional treatments such as antihistamines remain the first line of management, but advances in biologic therapies, particularly omalizumab and emerging monoclonal antibodies targeting specific immunological pathways, have shown remarkable efficacy in refractory cases. This article reviews the pathophysiology, diagnostic criteria, and the latest developments in targeted therapies for CU, highlighting their potential to improve patient outcomes.

Keywords: Chronic urticaria; Angioedema; Antihistamines; Omalizumab; Biologics

Introduction

Chronic urticaria (CU) is defined as the occurrence of hives and/or angioedema lasting for six weeks or longer. Affecting approximately 0.5–1% of the population, CU can occur at any age, though it is most common in adults between 20–40 years [1]. The condition can be classified into chronic spontaneous urticaria (CSU), where no external trigger is identified, and chronic inducible urticaria (CIndU), which occurs in response to specific stimuli such as pressure, cold, or heat. Although CU is not life-threatening, its chronic nature significantly affects physical comfort, emotional well-being, and social functioning.

Pathophysiology

The underlying mechanism of CU involves the activation of skin mast cells and basophils, leading to the release of histamine, leukotrienes, prostaglandins, and other inflammatory mediators. In CSU, autoimmune mechanisms are implicated in up to 45% of cases, where autoantibodies target either the high-affinity IgE receptor (FcεRI) or IgE itself. These autoantibodies stimulate mast cells to degranulate, causing the characteristic wheals and angioedema. Additionally, dysregulation of intracellular signaling pathways, enhanced mast cell sensitivity, and the influence of neuropeptides have been observed. In CIndU, external stimuli activate mast cells through physical or chemical triggers rather than autoimmune pathways [2].

Diagnosis

Diagnosis of CU is largely clinical and depends on patient history, symptom duration, and exclusion of other causes of urticaria. A detailed history should assess potential triggers, duration of lesions (usually <24 hours for individual wheals), associated angioedema, systemic symptoms, and response to medications. Common diagnostic steps include:

Physical examination: Assessing skin lesions and ruling out differential diagnoses such as urticarial vasculitis.

Laboratory tests: CBC, ESR/CRP, thyroid function tests, and autoimmune screening for suspected autoimmune CU.

Challenge tests: Used in CIndU to reproduce symptoms with suspected triggers (e.g., ice cube test for cold urticaria).

Exclusion of systemic disease: Through relevant imaging or serological tests when clinically indicated [3].

Management

Management of CU focuses on symptom relief, trigger avoidance (in CIndU), and improving quality of life. Treatment is typically stepwise, based on international guidelines such as EAACI/GA²LEN/EDF/WAO:

First-line therapy: Non-sedating, second-generation H1-antihistamines (e.g., cetirizine, loratadine, fexofenadine) taken daily, rather than as needed.

Second-line therapy: Increasing the antihistamine dose up to fourfold in non-responders.

Third-line therapy: Addition of biologic agents such as omalizumab (anti-IgE monoclonal antibody) for refractory cases. Omalizumab has been shown to significantly reduce symptoms and improve quality of life scores [4].

Alternative therapies: Cyclosporine for severe, unresponsive cases due to its immunosuppressive properties. Leukotriene receptor antagonists (montelukast) can be used as adjunct therapy.

Adjunct measures: Lifestyle adjustments, patient education, and stress management, as stress can exacerbate CU.

Advances in targeted therapies

Recent developments in biologic therapies have revolutionized the treatment of refractory CU.

Omalizumab: Administered subcutaneously every 4 weeks, omalizumab binds to circulating IgE, preventing its interaction with

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FcεRI receptors on mast cells and basophils. It has an excellent safety profile and is highly effective in both CSU and some CIndU cases [5].

Ligelizumab: A newer, high-affinity anti-IgE monoclonal antibody currently in advanced clinical trials, showing promising results with potentially longer-lasting effects than omalizumab.

Anti-IL-5 and anti-IL-4/IL-13 therapies: Targeting eosinophilic and Th2-mediated pathways for patients with overlapping atopic conditions.

BTK inhibitors: These small molecules inhibit Bruton's tyrosine kinase, which plays a role in mast cell activation.

Discussion

While antihistamines remain the cornerstone of CU management, the advent of biologics has transformed outcomes for patients with treatment-resistant disease. Omalizumab has set the standard for targeted therapy, but ongoing research may soon expand the arsenal with ligelizumab and other novel agents. One challenge is the high cost of biologics, which limits accessibility, particularly in low-resource settings. Future strategies may focus on identifying biomarkers to predict treatment response and personalizing therapy accordingly. In addition, psychological support and counselling are essential, as CU is associated with higher rates of anxiety, depression, and sleep disturbances.

Conclusion

Chronic urticaria is a complex dermatological condition with a multifactorial etiology involving immune dysregulation and mast cell activation. Advances in targeted therapies, especially anti-IgE monoclonal antibodies, have significantly improved symptom control in refractory cases. Ongoing research holds promise for more effective, long-lasting, and affordable treatments. Clinicians must adopt an individualized approach, balancing efficacy, safety, cost, and patient preference to optimize outcomes.

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