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Chronic Idiopathic Urticaria

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Abstract

Urticaria, often known as hives, is a common cutaneous illness that affects between 15% and 25% of the population at some point in their lives. The purpose of this research was to compare the serum Claudin-3 levels of patients with chronic urticaria to those of healthy controls and to determine whether or not there was a correlation between the two. Methods: Fifty patients with chronic urticaria were recruited from the Dermatology outpatient clinic at Benha University Hospital, and thirty healthy persons were recruited to serve as a control group and were matched with cases for age and sex. The Benha Faculty of Medicine's Research Ethics Committee on Research Involving Human Subjects gave its stamp of approval for the study to proceed. All contributors voluntarily provided informed consent. Claudin 3 serum levels were found to be significantly higher in the sick group compared to the control group. Increases in claudin 3 levels are positively correlated with severity. Claudin 3 levels were the only ones investigated as a potential predictor of CU severity. Claudin 3 has a highly correlated favourable relationship with UAS. Claudin 3 levels were found to be considerably greater in CU patients compared to healthy controls. The presence and quantity of Claudin 3 are both risk factors for developing CU and indicators of the severity of the disease.

Keywords: Serum Claudin 3, Chronic Idiopathic, Urticaria.

1. Introduction

Conventionally, wheals that occur often, on most days of the week, over duration of six weeks are what are meant by the term "chronic urticaria" (CU). Both chronic idiopathic urticaria (also known as chronic spontaneous urticaria) and chronic inducible urticaria (CU) are subtypes of CU (also called physical urticaria). Acute uveitis (CU) is a self-limiting, spontaneous condition in most cases [1].

Eighty percent to ninety percent of both adults and children with CU have chronic idiopathic urticaria. Patients with persistent idiopathic urticaria develop lesions for no apparent reason. It is fairly unusual for a patient to have both chronic idiopathic urticaria and chronic inducible urticaria at the same time. Idiopathic CU accounts for the vast majority of cases. In some of these patients, autoimmunity is thought to play a key role in the development of urticaria [3] Medications: Several medications, including aspirin and other nonsteroidal anti-inflammatory drugs, opioids, ACE inhibitors, and alcohol, have been linked to the development of urticaria or have been shown to exacerbate its symptoms. In 6.7%-67% of people, aspirin may worsen CU symptoms. Alcohol, opioids (codeine, morphine), and oral contraceptives are also suspected. The Four Types of Contactants

Urticaria that develops 30-60 minutes after interaction with a trigger substance is known as contact urticaria syndrome. You might have localised or systemic lesions. Latex (particularly among healthcare professionals), plants, animals (e.g., caterpillars, dander), drugs, and food may all play a role in triggering an allergic reaction (eg, fish, garlic, onions, tomato) [8]

Brain-related variables

CU was linked to an increased risk of fibromyalgia. The authors hypothesised that fibromyalgia-neurogenic skin inflammation is to blame for CU (7).

Stress

Several individuals have indicated that psychological elements contributed to their condition. Decreased levels of dehydroepiandrosterone sulphate are linked to emotional suffering, as shown in CU. Additionally; depression has been linked to the development of CU. [6]

Foods

The prevalence of pseudo-food allergy was estimated to be between 1% and 3% by Di Lorenzo et al., who examined 838 individuals with chronic/recurrent idiopathic urticaria. In double-blind, placebo-controlled provocation experiments, the following drugs were used: tartrazine (E102), erythrosine (E127), monosodium benzoate (E211), phydroxybenzoate (E218), metabisulfite (E223), and monosodium glutamate (E226) (E620). In instances with CU/refractory angioedema that do not react well to H1-antihistamine therapy, the authors suggest evaluating the potential of exclusion diets and provocation testing with food additives. The majority opinion on CU is that dietary additives may contribute to the condition but are seldom the lone cause [5]

Thyroid disease and persistent urticaria

Idiopathic CU has been linked to the autoimmune diseases Hashimoto's thyroiditis and Graves' disease.

Patients with idiopathic CU have impaired thyroid function in 19% and have antithyroid antibodies in 27%.

High titers of antithyroid antibodies (antithyroglobulin and antiperoxidase) may be found in such CU cases, although only 3% to 4% of the general population without thyroid problems has such antibodies. [9]

Chronic urticaria caused by an autoimmune response

Idiopathic, or "spontaneous," CU still accounts for 50-60% of all instances.

Recently, several authors have shown that elevated expression of coagulation tissue factor on eosinophils triggers thrombin production in individuals with CU. This identifies a plausible cause of the observed improvement in vascular permeability. Serum indicators of coagulation and fibrinolysis, such as fragment 1+2 prothrombin and D-dimer, are often high in these individuals, and their levels seem to be correlated with the severity of CU [8] Thrombin increases capillary permeability in animal models by both direct and indirect mechanisms, including impact on the endothelium, increased C5a without C3, and complement cascade bypass. Some individuals with chronic urticarial may have increased symptoms due to a synergy between the activity of autoantibodies and the coagulation cascade [7].

Pathogenesis:

IgE autoantibodies against auto-allergens or IgG autoantibodies targeting the high-affinity receptor Fc-epsilon-RI and/or IgE on mast cells have both been implicated as causes of chronic idiopathic urticaria. Due to the higher prevalence of thyroid problems and thyroid autoantibodies in CU patients, the term "autoimmunity" was coined to describe this phenomenon [6]

About half of CU patients develop autoantibodies against the IgE portion of the receptor or IgE itself, which causes mast cells to degranulate. Some people with CU have autoantibodies, and they are most often discovered to be mast cell-activating autoantibodies. [2]

In addition to other inflammatory cytokines, interleukin 3 (IL-3) has been linked to urticaria's development. Evidence suggests that IL-3 and TNF-alpha expression is increased in both lesional and uninvolved skin in various kinds of urticaria. Possibly through causing subthreshold inflammation in endothelial cells of uninvolved skin, cytokines contribute to the pathophysiology of urticaria. Increased histamine production in response to an anti-IgE stimulation and a hyper-responsiveness to IL-3 are hallmarks of chronic urticaria [10]

Proteins released by mast cells

Mast cell involvement is supported by findings of mast cell degranulation in tissue biopsies, an increase in histamine content in skin lesions caused by over-the-counter eczema treatments, and a positive clinical response to antihistamines. The issue of whether or whether CSU sufferers have more cutaneous mast cells is still up for debate. Some research showed a rise, while others found levels to be about the same as in healthy skin. Mast cell presence is also inferred indirectly by total serum tryptase levels, which are elevated relative to both atopic and nonatopic controls but still fall within the normal range [5]

Although the average tryptase is greater in individuals with CSU who report just skin-limited symptoms, it is higher in those who also express extracutaneous systemic symptoms. Different receptors on mast cells are readily activated (eg, chemokine, prostaglandin, Toll-like, or immunoglobulin receptors). Mast cell activation in chronic idiopathic urticaria (CSU) is still poorly understood. Subjects with CSU have an increased risk of developing autoimmune disorders [3].

Plasma factors

The expression of autoreactive IgE species that activate cutaneous mast cells in CSU is a second autoimmune explanation. Consider the hypothesis that people with CSU have higher than average levels of IgE directed towards thyroid peroxidase [4]

Cascade of coagulation

As mentioned above, there is evidence that people with CSU have activated coagulation cascades. When blood vessel walls are breached, tissue factor is released, setting off the extrinsic cascade. Proinflammatory mediators may be amplified because various active parts of this coagulation cascade can activate protease-activated receptors on various cell types [1]

These findings are in keeping with the hypothesis that bradykinin serves as a mediator in hereditary angioedema, where the same prothrombin fragment 1-2 and D-dimer are raised in individuals [3]

Hereditary angioedema does not include mast cells, basophils, or eosinophils, and it does not cause urticaria. It's possible that the common denominator is endothelial cells that have been activated [4] Basophils

The importance of basophils in CSU pathogenesis is being more well supported. Basophils have IgE receptors and may produce histamine and cytokines including IL-4, IL-13, and IL-31 in response to IgE receptor activation [10]

Basophil degranulation of histamine in response to anti-IgE is diminished in patients with active CSU, and basophils infiltrate skin wheals in a way that is not seen in individuals with latent or inactive CSU.

CSU responder (>10% release of total histamine content) and CSU nonresponder (10% release of total histamine content) are two unique basophil functional phenotypes based on IgE receptor driven histamine release patterns. Increased expression of intracellular phosphatases, which control IgE signalling pathways critical for histamine release, seems to be the cause of the aberrant response, but other routes for degranulation are unaffected (Nformyl-met-leu-phe [FMLP], monocyte chemoattractant protein 1)

2. Patient and Methods

Clinical presentation

Wheals have three typical features (Figure **1)**

- Central edema of variable size, almost always surrounded by a reflex erythema
- Association with pruritus and sometimes a burning sensation,
- Ephemeral nature, with the skin returning to its regular appearance in usually 1 to 24 hours.
- Angioedema is characterized by:
- A sudden, pronounced edema of the deep dermis and subcutaneous tissue;
- Pain more often than pruritus
- Frequent involvement of mucous membranes
- Resolution of symptoms in about 72 hours, more protracted than in the case of wheals.

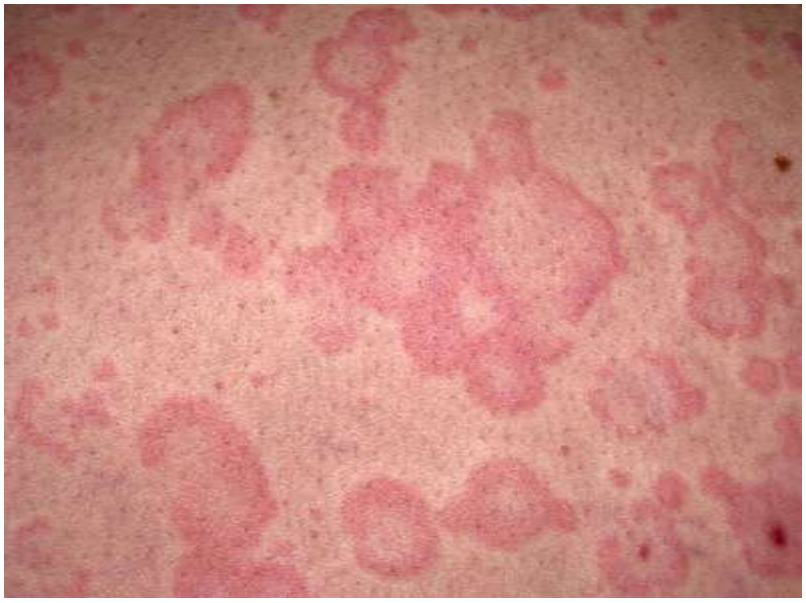


Fig. (1) Urticarial wheals ***(Schaefer, 2017).***

Diagnosis

Routine inquiry should involve a solid history, a comprehensive physical examination, searches for information on suspected causation variables, and vital data on the type of urticaria because of the enormous variety of this group of disorders termed urticaria.

Laboratory

If a clinical history and physical examination suggest the presence of a potentially life-threatening systemic condition, further diagnostic testing is required.

Screening tests that may be performed to rule out a condition of unknown cause include the C-reactive protein (CRP)/erythrocyte sedimentation rate (ESR) and the complete blood count (CBC) with differential.

Patients with chronic urticaria often have normal results on a total blood cell count. An allergy or parasite infection can be to blame for the elevated eosinophil count. An underlying systemic condition such an autoimmune, rheumatologic, viral, or neoplastic disease is likely when C- reactive protein/erythrocyte sedimentation rate levels are significantly elevated.

Indicative of thyroid illness is a serum TSH level above or below the normal range. If urticarial vasculitis is suspected, serum complement levels should be checked since individuals with it often have low levels of C1, C1q, C2, C3, and/or C4.

Autologous serum skin testing and measurement of IgG-anti-FceRI, IgG-anti-IGE, total IgE, IgE anti-self, and other autoantibodies in the blood are also valuable. Recent research has shown a correlation between children with reduced basophil levels and quicker recoveries.

To do a biopsy on the skin

If vasculitis or urticaria vasculitis is suspected, a skin biopsy of wheals should be conducted since these lesions may last for more than 24 hours in the same spot and often leave hyperchromic or purple residual lesions.

Patients may also describe burning sensations, either alone or in conjunction with pruritus. In situations when antihistamines have failed to alleviate symptoms, a skin biopsy of wheals may be necessary as well.

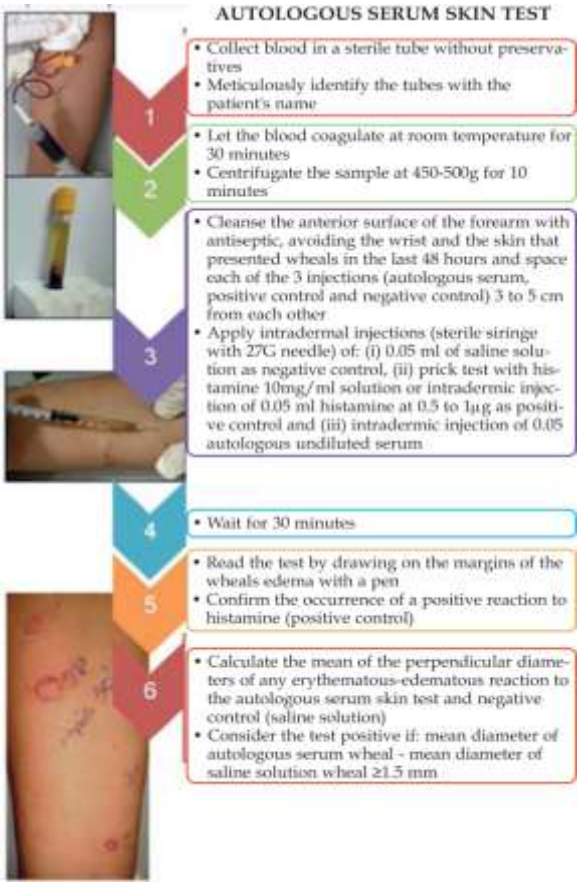
Autologous serum skin testing: some things to think about (ASST)

Individual autoreactivity may be evaluated with the use of a "in vivo" test called the autologous serum skin test (ASST).

Intradermal injection of autologous serum (obtained from the patient during the clinical activity of urticaria, or crisis) causes an autoreaction characterised by wheals and pruritus by acting either indirectly through the release of mediators from mast cells/other cells or directly on the skin's microvasculature. It's important to note that autoantibodies in the autologous serum of patients with CU and a positive skin test aren't definitive evidence of autoimmune urticaria, although they may be indicative of mast cell activation. ASST

Algorithm 1 is a summary of suggestions for standardising ASST's methodology.

An ASST requires the patient to abstain from histamine-suppressing medications for a time period that varies by patient.



Algorithm (1) Method of execution of the autologous serum skin test :

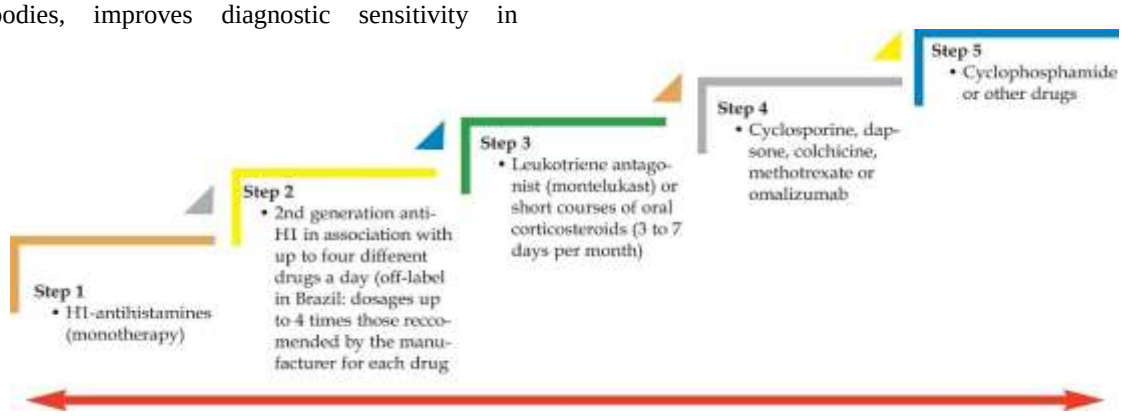
1. Considerations on the autologous plasma skin test (APST)

The autologous serum skin test is basically a diagnostic method used in autoimmune CU that is based on the intradermal injection of autologous serum. Coagulation factors and sodium citrate may be found in the plasma utilised in the APST. Therefore, autoantibodies that promote thrombin activity and/or the sodium citrate may both contribute to APST positive.

Asero et al. (2006) studied 96 individuals with CU and found that 53% of them were ASST-positive, whereas 86% of those tested with the APST-positive. The Italian research team led by Dr. Asero proposes that the autologous plasma skin test, which demonstrates the activation of the coagulation cascade in the presence of autoantibodies, improves diagnostic sensitivity in instances with autoreactive CU. These autoantibodies stimulate the coagulation cascade and compensatory fibrinolysis by degranulating mast cells and basophils, activating eosinophils, and ultimately releasing tissue factor. As a consequence of fibrinolysis, thrombin is produced, which in turn activates additional mast cells and the vascular endothelium, and more d-dimers are also found.

Treatment

In most people, it is unclear what causes their chronic urticaria, and some instances clear up on their own. Symptomatic relief is the primary focus of treatment. Many drugs for the treatment of CU have been reported, while second-generation H1 antihistamines are the first line of therapy (Algorithm 2)



Algorithm (2) Sequential treatment of Chronic Urticaria (in steps)

Antihistamines

Symptomatic therapy with H_1-antihistamines is the mainstay of treatment for the vast majority of CU patients. Continuous use of H_1-antihistamines in CU is supported not only by the results of clinical trials, but also by the mechanism of action of these medications. These drugs are inverse agonists with preferential affinity for the inactive state of the histamine H_1-receptor and stabilize it in this conformation, shifting the equilibrium toward the inactive state (٤).

Many guidelines recommend modern second-generation H_1-antihistamines as a first-line symptomatic treatment for CU and suggest up-dosing second-generation H_1-antihistamines up to 4-fold in patients with CU unresponsive to standard doses (**Table 3**) [2]

Table (3) Differences between first and second-generation anti-H1

First-generation H1Antihistamines	Second-generation H1Antihistamines
Usually given 3 to 4 times a day	Usually given once or twice a day
Cross the blood-brain barrier (they are lipophilic substances, have low molecular weight and are not substrates of the P-glycoprotein efflux pump system)	Do not cross the blood-brain barrier (they are lipophobic substances, have high molecular weight, and are substrates of the P-glycoprotein efflux pump system)
Cause several adverse events (sedation, hyperactivity, insomnia and seizures)	Do not cause significant adverse events in the absence of drug interactions
Case reports on toxicity are regularly published.	Reports on serious toxicity events are virtually non-existent.
Absence of placebo-controlled, randomized, double-blind clinical trials	Some placebo controlled, randomized, double-blind clinical trials, even in children
Lethal dose already identified in infants and children	No report of fatality due to overdose

3. Results

Demographic data among studied groups were shown in **Table 1.**

Risk factors were assessed among all studied subjects, 22% were smokers, 36% had positive family history, 16% reported history of drug intake, 16% used to use food additives, 14% had psychological problems and 10% had positive H pylori. Patient group was significantly associated with positive family history when compared to control group (p=0.011). Otherwise, no significant association was found regarding risk factors among studied groups (p>0.05 for each). **Figure 2**

Table (1) Comparison of demographic data among studied groups.

		Control group N=30		Patient group N=50		p
Age (years)	**Mean ± SD**	37	9.5	34.6	11.1	0.345
Males	**N, %**	12	40%	16	32%	0.468
Females	**N, %**	18	60%	34	68%	

SD, standard deviation.

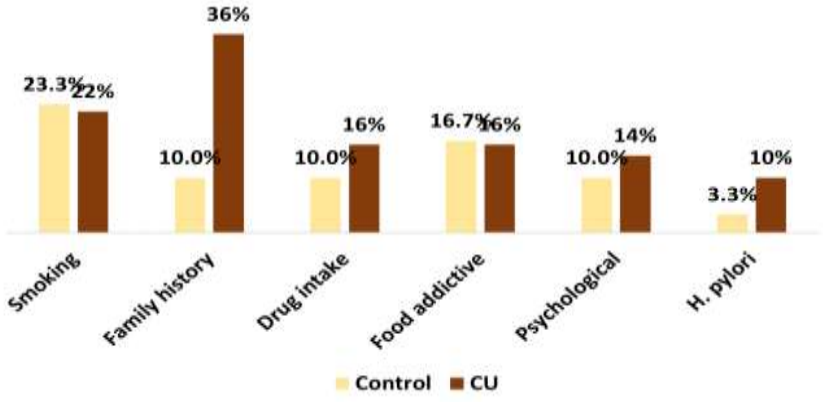


Fig. (2) Risk factors among studied groups.

4. Discussion

The vast majority of recommendations endorse this approach. Higher dosages of H1-antihistamines have shown greater effectiveness in many individuals, and this strategy is supported by clinical research [10]

H2-antagonists and leukotriene receptor antagonists are not recommended in the treatment algorithm from the recent European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA2LEN)/European Dermatology

Forum (EDF)/World Allergy Organization (WAO) guideline because of the lack of supporting scientific evidence. Despite their limited effectiveness and low safety profile, H2-antagonists and leukotriene receptor antagonists are nonetheless recommended for usage in stages 2 and 3.

A brief course of oral corticosteroids, no more than 10 days, is therapy for acute urticaria and acute exacerbations of CSU [8]

Since omalizumab (Xolair; Genentech/Novartis, South San Francisco, CA, USA) has been shown to be effective in double-blind, placebo-controlled trials, the revised EAACI/GA2LEN/EDF/WAO guideline advises using it as step 3 treatment for patients who have not responded to H1-antagonists. (1) By binding to free IgE, omalizumab decreases free IgE levels, which in turn down-regulates FcRI receptors on basophils and mast cells. [5] The timing for reduction of IgE receptors is substantially sooner for blood basophils than for skin mast cells. This differential down-regulation of IgE receptors, first seen in allergy patients, has been replicated in CSU participants. Reducing mast cell releasability, reversing basopenia and improving basophil IgE-receptor function, decreasing the activity of IgG autoantibodies against FcRI and IgE, decreasing the activity of IgE autoantibodies against antigens or autoantigens that have not been definitively identified, decreasing the activity of intrinsically 'abnormal' IgE, and decreasing in vitro coagulation abnormalities associated with disease a Improving CSU symptoms by a large margin, omalizumab's mechanism of action remains unclear [2]

5. Conclusion

Patients with CU had considerably greater levels of Claudin 3 compared to healthy controls. The presence and quantity of Claudin 3 are both risk factors for developing CU and indicators of the severity of the disease. Current findings implicate claudin 3 in the pathogenesis of chronic urticarial. This work has the potential to pave the way for future research and clinical trials that confirm or refute a connection between claudin 3, gut barrier integrity, and the immune system in additional autoimmune illnesses.

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