Review Article

Assessment of Autoimmunity in Urticaria

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ABSTRACT

Urticaria is distinguished by the sudden onset of temporary, pruritic skin swellings (wheals). It is believed that autoimmunity, or more specifically, autoimmune mechanisms of cutaneous mast cell activation, is a prevalent underlying cause of CSU. An elevated odds ratio for hypothyroidism, hyperthyroidism, and the presence of thyroid autoantibodies was linked to a diagnosis of CU. About 50% of patients have positive "autoimmune" tests in vivo and/or in vitro, and there is a substantial quantity of circumstantial evidence indicating that chronic urticaria is an autoimmune illness. While there are still many unanswered questions regarding CSU, it is becoming more and more obvious that both autoimmunity (an IgG-mediated disease) and autoallergy (an IgE-mediated disease) can play a role in its pathogenesis and predispose individuals to the emergence of other autoimmune diseases.

Keywords: CSU (chronic spontaneous urticaria), CU (chronic urticaria), CIU (chronic idiopathic urticaria), (ASST) autologous serum skin test.

INTRODUCTION

Urticaria is distinguished by the sudden onset of temporary, pruritic skin swellings (wheals) of alterations to the skin[1]. Urticarial wheals are flat, edematous, perceptible spots that range in color from porcelain white to light crimson and have a variety of sizes and shapes[2]. Histamine and other preformed and newly generated vasoactive proteins and mediators are released by mast cells and basophils under regulated conditions, which results in the development of wheals[3] .

Hives are not caused by any known specific antigen, and both nonatopic people and those with a personal or familial history of allergic rhinitis, asthma, or eczema (atopic dermatitis) are equally likely to have them[4],15% to 25% of people will get urticaria at some point in their lives[5].The illness often occurs at its highest rate in one's third to fifth decade of life and is more common in adults than in children and women than in males.

Infections, dietary intolerance, the coagulation cascade, genetic factors, and autoimmune have all been looked studied as potential pathogenesis factors for CSU[3],because it has been demonstrated that exposure to phthalates—substances primarily used to soften polyvinyl chloride—increases children's risk for developing acute urticaria[5]. In allergic disorders, notably urticaria, a chronic condition with a low death rate, quality of life (QoL) is crucial. Urticaria is a common condition, but because of how much it affects sufferers' daily lives, it is also a social and economic burden[6] .

A wide range of everyday tasks, including personal care, sleep/rest, work performance, and social interactions are impacted by CU symptoms (such as itching and wheals). Beyond the intensity of the actual disease symptoms, physical and emotional functioning is subjectively hampered[7]. It can be roughly divided into acute and chronic types. Over two-thirds of instances of urticaria are categorized as acute, which is defined as bouts lasting shorter than six weeks. There are situations when an allergic or viral trigger is found. 30% of instances of urticaria are chronic, characterized as bouts lasting longer than six weeks[1].

There are three main urticaria subgroups that should be distinguished according on duration and triggers: i) Physical urticaria; ii) spontaneous urticaria; and iii) additional specific forms Exogenous elements like cold, pressure, heat, and vibration can cause certain types of physical urticaria. Other different kinds include cholinergic urticaria, aquagenic urticaria, contact urticaria, urticarigenic substance contact, and exercise-induced urticaria. Cholinergic urticaria is produced by a rise in body temperature, whereas aquagenic urticaria is activated by water. In any given patient, two or more urticaria subtypes may coexist[8].

CU can also be divided into chronic autoimmune urticaria (45%) and chronic idiopathic urticaria (CIU) (55%)[9].Chronic spontaneous urticaria (CSU) is a mast cell–driven skin disease characterized by the recurrence of transient wheals, angioedema, or both for more than 6 weeks[9]. In contrast to angioedema, urticaria is characterized by recurring bouts of oedema in the skin, mucous membranes, gastrointestinal tract, and respiratory tract. Although the swelling may linger for days, angioedema is not itchy. A functional deficit of the complement's first activated component is what causes angioedema[10].

Several illnesses that either increase the risk of developing the condition or promote mast cell degranulation are linked to CSU[11]. Immune dysregulation in CU is defined by a systemic inflammatory profile linked to aberrant

production of cytokines and immunoglobulin (Ig) E by B cells. One of the most common causes of CSU is assumed to be autoimmune disease[12]. The presence of functional and pertinent mast cell-degranulating IgG autoantibodies against IgE or its high-affinity receptor FcεRI is used here to identify autoimmune chronic spontaneous urticaria (aiCSU). The etiology and pathology of CSU have been linked to type I and type II autoimmunity (i.e., IgE to autoallergens and IgG autoantibodies to IgE or its receptor, respectively)[3] IgE-mediated Type I autoimmunity, also known as autoallergy, may have a role in this[13].

The idea for Type IIb autoimmunity in CSU was first sparked by observations that intradermal injections of autologous sera resulted in a wheal. The autologous serum skin test (ASST) is presented here[13].In order to promote a multidisciplinary and multimorbid approach to the patient with CSU, this review sought to analyze the close relationship between CSU and some autoimmune and autoinflammatory diseases. This allowed control over the disease's natural course as well as any associated comorbidities[14], additionally, the discovery of an autoimmune cause can aid in removing the necessity for further investigation into other etiologies[12]

URTICARIAL VASCULITIS

A type III hypersensitivity reaction, urticarial vasculitis is a rare clinicopathologic condition that appears as a result of an inflammatory slander to the small blood vessels of the skin. It is believed to be immune-complex mediated[15].The majority of patients have no apparent etiology, but recognized etiological factors including paraproteinemia and viral diseases like hepatitis B and C and HIV are present.

Additionally, ulcerative colitis, Crohn's disease, or ulcerative vasculitis may be the first or very first clinical manifestation of an autoimmune disease (lupus, Sjogren's syndrome). Occasionally, drug hypersensitivity may also be a factor[16]. In a distinct subset of patients with chronic urticaria and vasculitis, immune complexes, complement activation, anaphylatoxin production, histamine release, and neutrophil accumulation, activation, and degranulation are likely to play a role in the development of hives[17],Pruritic, burning, or excruciatingly elevated, superficial, erythematous, or edematous, circumscribed wheals with purpura and induration are the hallmarks of urticarial vasculitis (UV)[18].

Despite the fact that the majority of UV cases have no known cause, UV can be linked to certain medications, infections, autoimmune and autoinflammatory illnesses, or malignancies[19]. Urticarial vasculitis(UV) accounts for up to 5% of CU cases and is mediated by immune complex deposition in blood vessel walls [1]

The diagnosis is supported by a skin biopsy that reveals leukocytoclastic vasculitis, or more precisely, venulitis. Secondary urticarial vasculitis is the term for urticarial vasculitis that develops as a symptom of another condition, such as SLE or another collagen vascular disease. Primary or idiopathic UV is a diagnosis of exclusion, similar to chronic idiopathic utricaria, and can be further divided based on serum complement levels[20].

It is separated into normocomplementemic (normocomplementemic urticarial vasculitis, NUV) and hypocomplementemic (hypocomplementemic urticarial vasculitis, HUV, and HUVS, McDuffie syndrome) categories[19]. Leukocytoclastic vasculitis and perivascular immunoglobulin, complement, and fibrin deposition are found in skin biopsy results for both histology and direct immunofluorescence. Hypocomplementemia (C3,C4), elevated inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), and a positive antinuclear antibody are all possible results of laboratory testing [1] H1-antihistamines have a poor therapeutic effect in urticarial vasculitis. Other medications that have been suggested include colchicine, dapsone, and antimalarials. Systemic steroids may be helpful, although systemic problems are almost always a given given the disease's typically lengthy course[16]

PATHOPHYSIOLOGY

Although the pathogenic processes of chronic (CU) are not fully known, activation of cutaneous mast cells is crucial for the inflammation that results from the condition. Histamine in particular can contribute to cutaneous inflammatory processes and the accumulation and activation of other cells when mast cells are activated and release mediators.

Also circulating cells, possibly basophils and platelets, may play a relevant role in urticaria[21], mast cell degranulation can be triggered by immunological or nonimmunological factors[22]. recent research on urticaria revealed that various immune cells, including basophil degranulation, eosinophils, T and B lymphocytes, epithelial, and endothelial cells, are also implicated[14]. Incomplete degranulation in allergic urticaria is caused by the cross-linking of two or more adjacent allergen-specific immunoglobulin (Ig) E molecules that are attached to the high affinity IgE receptor (FcεRI) on mast cells or basophils.

This process is triggered by intracellular calcium-dependent signaling processes. Histamine is released in vitro by autoantibodies against IgE, FcεRI, or both on basophils and mast cells, which is assumed to be the underlying cause of autoimmune urticaria. This process might be complement (C)-dependent, because in the lab, C5a is a powerful degranulating agent[22].

The majority of individuals in the subset of positive patients who had been thoroughly researched were discovered to have an IgG antibody directed against the a component of the IgE receptor. It was possible to demonstrate the release of histamine or the enzyme-hexosaminidase using rat basophil leukemia cells that had been transfected with human a subunit. Thus, it appeared that the antibody may cross-link a subunit of the IgE receptor and cause the cells to granulate[17].

In order to activate mast cells and basophils and trigger the release of histamine and other pro-inflammatory mediators, anti-FcεRI and anti-IgE antibodies are both able to directly cross link neighboring FcεRI receptors. Additionally, autoantibody attachment to receptors triggers the complement cascade, which creates anaphylaxis-causing toxins[23]

ETIOLOGY

Acute urticaria can be brought on by food allergies, which are more common in young children and infants. In adulthood, food allergies are less frequently the cause of urticaria. Peanut butter, strawberries, cow's milk, fish, and eggs are examples of common dietary allergens. Most dietary allergies result in urticaria within 30 minutes of consumption, and the reaction is repeatable[10] infection- Urticaria in kids is frequently brought on by viral infections. Additionally, bacterial infections like Escherichia coli can cause urticaria[10]

bites – mosquitoes, sandflies, pet fleas

drug intake- consumption of both prescribed and illicit drugs. In particular, urticaria can be brought on by angiotensin converting enzyme (ACE) inhibitors, laxatives, aspirin, nonsteroidal anti-inflammatory medications (NSAIDs), codeine, and antibiotics[10]

physical causes- Urticaria can be caused by physical factors such as exposure to cold, pressure, vibration, exercise, and sunlight[10]

CLINICAL PARAMETERS

The recurrence of wheals more than twice a week for a minimum of six weeks is known as CU. CU also has a variety of additional traits, including: -

Simple dermatographic urticaria differs from wounds lasting longer than an hour, and urticarial vasculitis differs from wounds lasting longer than 24 to 36 hours. Inflamed and painful lesions are possible with outbreaks and remissions that can span from a few months to more than 20 years, the disease's natural history varies widely. major QoL effects that are thought to be comparable to those in severe coronary disease[7]. Anywhere on the body, urticarial lesions are polymorphic, pruritic cutaneous wheals that can range in size from a few millimeters to a few centimeters. Individual lesions typically disappear within 24 hours[24]

AUTOIMMUNITY IN UTRICARIA

It is believed that autoimmunity, or more specifically, autoimmune mechanisms of cutaneous mast cell activation, is a prevalent underlying cause of CSU. Gell and Coombs hypersensitivity reactions of two different types have been suggested to be significant in autoimmune CSU patients[25]

The presence of functional and pertinent mast cell-degranulating IgG autoantibodies against IgE or its high-affinity receptor FcεRI is used here to identify autoimmune chronic spontaneous urticaria (aiCSU)[1] Clinically, the rise in autoimmunity in CSU points to a dysfunctional immune system and an unbalanced ratio of pro-inflammatory T17 cells to T regulatory cells (Tregs). Numerous systemic and organ-specific autoimmune disorders may be attributed to the dysfunction of T regulatory cells (Tregs), particularly T follicular regulatory cells, which results in the survival of autoreactive T and B cells and altered dendritic cell antigen presentation[11]

Because autoimmune disease can affect the entire body, not only the skin, CU may develop in systemic involvement or be linked to other autoimmune disorders. According to several research, comorbidities are frequently present in CU patients. However, the majority of these research looked at how CU and mental illnesses such depression, anxiety, and behavioral issues interacted[26]

The issue of autoimmunity in CU was originally brought up by the finding that a higher-than-expected percentage of CU patients have autoimmune thyroid illness. Since then, additional circumstantial evidence has accumulated that links an autoimmune process; Studies at a subcellular level have revealed abnormalities in the p21-Ras pathway (involved in regulating inflammation) in patients with CU, which have been described as a characteristic of other autoimmune diseases, such as type 1 diabetes mellitus and SLE.

Immunogenetic studies have found an increased prevalence of the autoimmune associated alleles human leucocyte antigen DR4 and DQ8 in patients with CU[24]. The alpha-chain of the high affinity IgE receptors (FcεRI) produced on cutaneous mast cells or blood basophils is the target of IgG autoantibodies in the majority of individuals with autoimmune chronic urticaria (Niimi et al. 1996). By first incubating the basophil leucocytes of healthy donors with human recombinant alpha chain, histamine release induced by these antibodies can be suppressed. Regardless of IgE binding, some of them bind to FcεRI. However, IgE to varying degrees interferes with the binding of the majority of these forms of autoantibodies through competitive means (Hide et al. 1995). Histamine is released by the autoantibody when IgE is removed (by lactic acid stripping), but is inhibited when IgE is reconstituted on the surface of basophils (Niimi et al. 1996).

Witebsky's postulates were developed as a foundation for identifying autoimmunity as the underlying cause of a certain disease. These hypotheses include the following: 1) the presence of an autoantibody or cell-mediated immunity; 2) the identification of the antigen against which the autoantibody or cell-mediated immune response is directed; 3) the presence of an analogous autoimmune response in an experimental animal model; and 4) the emergence of a disease-like condition in the animal model. Recently, Wegener's granulomatosis was diagnosed using these criteria by Hewins et al[20]

TYPE I AUTOIMMUNITY

In order to explain urticaria-associated basopenia, Rorsman first proposed a type I hypersensitivity to self, also known as autoallergy, in which antigens crosslink the IgE on mast cells and basophils to release vasoactive mediators[25], it was postulated following observations of IgE autoantibodies to thyroperoxidase [1]

TYPE II AUTOIMMUNITY

After the discovery of IgG-AAbs against IgE in 3 of 6 patients with CSU, a Type II hypersensitivity reaction was initially hypothesized. This reaction occurs when antibodies, typically IgG or IgM, bind to antigen on a target cell. Grattan et al. in 1991 found these AAbs in patients whose sera caused a wheal-and-flare reaction when administered intradermally[25]

There have been accounts of autologous sera being injected intradermally, which sparked the theory for Type IIb autoimmunity in CSU. This procedure is known as an autologous serum skin test (ASST). Subsequent research revealed that basophil and mast cell degranulation were directly induced by IgG antibodies to the patient's own IgE or its high-affinity receptor (FcεRI), and are therefore thought to be directly related to the etiology of urticaria[1] and subsequently they demonstrated in vitro that circulating IgG against IgE and/or high affinity IgE receptor (FcεRI) may be responsible for the histamine-releasing activity of CIU sera[27]

ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

In a recent comprehensive retrospective database review, the relationship between chronic urticaria and other autoimmune disorders was investigated. The results revealed that an autoimmune diagnosis is frequently made within ten years following a CU diagnosis.

An elevated odds ratio for hypothyroidism, hyperthyroidism, and the presence of thyroid autoantibodies was linked to a diagnosis of CU. Additionally, rheumatoid arthritis, Sjogren's syndrome, celiac disease, type 1 diabetes, and systemic lupus erythematosus odds ratios were higher in women with CU[28].The discovery that intradermal injection of autologous serum produced acute wheal-and-flare responses in 60% of individuals with CIU supported the hypothesis of an autoimmune background. The IgG autoantibodies anti-IgE and anti-FcRI were found in sera from 45% to 55% of patients with CIU, according to further research[29]

A growing amount of research is showing that some CIU sufferers have thyroid autoimmunity. According to the earliest investigations on autoimmunity in CIU patients, the condition is associated with a higher incidence of Hashimoto thyroiditis. Even in euthyroid patients, the correlation was shown to be with the existence of antibodies to thyroglobulin or a microsomal derived antigen (peroxidase)[17]

THYROID DISEASES

Thyroid autoimmune illness has been associated with chronic urticaria for a long time. In 2009, a study performed by Gangemi S. et al. found that one third of patient diagnosed with chronic idiopathic urticaria were positive for at least one thyroid autoantibody[26].

There is a link between urticaria and Hashimoto's thyroiditis, and a subset of people with chronic urticaria tend to have an autoimmune condition. About 24% of chronic urticaria patients have thyroid autoantibodies, and 19% of patients show biochemical signs of thyroid dysfunction[30].While they are found in just 5% of age-matched patients, antithyroglobulin and thyroid peroxidase antibodies have been detected in about 15% of patients with chronic autoimmune urticaria.

Furthermore, there may be an association between chronic autoimmune urticaria and thyroid dysfunction, with 5% of these patients as opposed to 1% of the background patients having an abnormal (usually increased) thyroid stimulating hormone (TSH). Treatment with thyroxine has been reported to occasionally result in a remission of urticaria with a normalization of the ASST in the subset of CU patients who are thyroid autoantibody positive (whether hypothyroid or euthyroid)[24]

Even in euthyroid patients, the correlation was shown to be with the existence of antibodies to thyroglobulin or a microsomal derived antigen (peroxidase). the frequency of either increased or decreased thyroxine (T4), increased or decreased thyroid-stimulating hormone (TSH), or both impaired thyroid function[17]

INFECTIONS

Since more than a century ago, discussions about the role of infections in urticaria subtypes have been addressed in most studies. 20–30% of children with spontaneous acute urticaria, 91% of which were brought on by infection, proceeded to chronic urticaria. The gastro-intestinal system, as well as the dental or ENT areas, are where chronic urticaria infections are most frequently observed[8].

Because of the development of immune complexes, simple viral infections frequently induce acute urticaria in children, although they are infrequently linked to the chronic form. Rare causes of CU include infection with germs, the human immunodeficiency virus, and parasite invasion [1]

Acute urticaria can be caused by viral infections in the Herpesviridae family, and cutaneous urticarial-like symptoms are linked to Herpesviridae reactivation[5] Numerous bacterial infections, including Helicobacter pylori, Streptococcus, Staphylococcus, Mycoplasma pneumoniae, Salmonella, Brucella, Mycobacterium leprae, Borrelia, Chlamydia pneumoniae, and Yersinia enterocolitica, have been linked to the appearance of urticaria. However, acute urticaria can also be encountered in conjunction with bacterial diseases such tonsillitis and cystitis[8].

In rare instances, the skin symptoms known as urticaria may be brought on by the microbe itself, its toxins, or complement activation mediated by circulating immune complexes [5]

DIAGNOSIS

There are no biomarkers currently on the market that can be used to assess and treat people with CSU. Basophil levels and susceptibility to activation, inflammatory indicators, markers of activation of the extrinsic coagulation cascade, immunoglobulin E, and vitamin D are potential biomarkers of CSU severity and/or duration [5]

URTICARIA ACTIVITY SCORE

The Urticaria Activity Score (UAS), which assesses the primary disease characteristics (itch, presence, and number of wheals) on a Likert-type symptom intensity scale (0 to 3), with a total daily score ranging from 0 to 6[7]. CU on a scale of 0 to 3 for symptom intensity (itch, presence, and quantity of wheals). Between 0 [none] and 3 [severe] for daily itching intensity and 0 [none] to 3 [more than 12] for daily wheals[7]

VISUAL ANALOG SCALES (VAS)

Visual analog scales (VAS) have also been utilized in adult and pediatric populations and have been validated for assessment of the severity, or intensity, of symptoms; however, VAS cannot be used to compare symptoms between different individuals[7]

AUTOLOGOUS SERUM SKIN TEST

In 30 to 50% of CIU, the autologous serum skin test (ASST) causes a rapid wheal-and-flare reaction When evaluating patients' autoreactivity in the first instance, ASST is thought to be extremely valuable. The existence of autoantibodies, which may be to blame for the degranulation of mast cells, is indicated by an erythematous and/or wheal-type skin reaction in response to the autologous serum [2]

When the red serum-induced wheal had a diameter that was at least 1.5 mm larger than the negative control wheal at 30 minutes, the ASST response was considered to be positive[13]The ASST is a test for the early detection of aiCSU that looks for any sort of histamine-releasing serum factor, such as IgG autoantibodies against FcεRIα or IgE.[31]

HISTAMINE RELEASE ACTIVITY (HRA) ASSAY

The HRA assay, which is equal to the CU index, detects ''functional'' autoantibodies and release factors by assessing histamine release when healthy basophils from a non-CIU population are incubated with the patient's serum. 10% or more indicates a positive CU index. The index value and the amount of histamine emitted are correlated[9]

BASOPHIL HISTAMINE RELEASE ASSAY

The goal of the serum-induced BHRA was to find IgE or high-affinity IgE receptor (FcεRIα)–directed autoantibodies in patient sera[13]

IgG ANTI-FCERIA

ELISA was used to find IgG antibodies to FcεRIα in control and CSU serum. A coating of FcεRIα (50 ng/mL; MyBioSource) was applied to ELISA plates[13]

IgG ANTI-IGE ANTI-IGE

antibodies were assessed by ELISA as described. Extinctions of >0.2 at 490 nm were considered positive[13]

IgG-ANTI-THYROPEROXIDASE (IGG ANTI-TPO) AND TOTAL SERUM IGE

Each study center used its own set of standardized protocols to quantify total serum IgE and IgG anti-TPO utilizing immunoassays or nephelometric analysis. The threshold value of 40 IU/mL was utilized to define a low IgE level(13)

NON PHARMACOLOGICAL TREATMENT

Even if the reason is unknown, acute urticaria often lasts a few days. Usually no therapy is necessary, however calamine lotion, antihistamines, and cold baths and compresses can provide temporary relief[10]

Avoiding physical triggers is advised. Similar to how those with exercise-induced anaphylaxis should never exercise, those with cold urticaria should be told never to swim. An auto-injector for adrenaline should also be prescribed for these patients. If at all possible, patients should cease using certain medications such aspirin, related nonsteroidal anti-inflammatory drugs, and opiates, which can either induce or exacerbate urticaria in some people. For certain patients, avoiding hot temperatures, spicy meals, or alcohol may be beneficial [1]

PHARMACOLOGICAL TREATMENT

Since a precise cause is typically not identified in CU instances, the main goal is to alleviate symptoms. Patients should be informed that pharmacological therapy may not totally cure their symptoms [1] CU treatment often proceeds empirically and in steps.

Treatment in autoimmune chronic utricaria

Cyclosporin may be helpful in people with resistant autoimmune chronic urticaria that is significantly disabling (Grattan et al. 2000). The dosage is 3–4 mg/kg/day for an average adult, and one of us typically recommends this dosage for two–three months.[1]

Oral antihistamines

Histamine released from mast cells causes urticaria symptoms, which are mostly mediated by H1 receptors on cutaneous nerves and endothelial cells. This means that the first line of treatment for CU is second generation, nonsedating antihistamines [1]such as fexofenadine 60 to

180 mg, loratidine 10 mg, cetirizine 10 mg, evastine 10 mg, etc., are typically used in the morning. It is beneficial to administer a second dose of the same antihistamine in the evening or just before going to bed because pruritus is most problematic in the evening and at night. A sedative antihistamine like hydroxyzine 25 mg may be recommended for people with severe nocturnal pruritus[16]

Oral corticosteroids

Prednisone is frequently prescribed to treat severe urticaria that does not respond to high dose antihistamines for a brief period of time. However, because of their negative side effects, corticosteroids cannot be used to treat CU over the long term [1]

Treatment of underlying systemic disease

Thyroid hormone replacement may help patients with hypothyroidism and thyroid autoantibodies. According to certain findings, euthyroid patients with CU and thyroid autoantibodies should additionally receive thyroxine treatment [1]

Treatments for histamine resistant disease

Many different drugs have been utilized to treat CU that did not respond to high dose antihistamines. They function as immunosuppressives, immunomodulators, and/or anti-inflammatory drugs[1]

DISCUSSION

The pathophysiology of chronic urticaria has been attributed to a number of interrelated causes. Unsuitable mast cell degranulation, with the release of already-formed mediators like histamine and newly-formed ones like leukotriene C4, D4, and prostaglandin D2, is essential to the pathophysiology of urticaria.

Numerous pathogenetic pathways, including immunological, autoimmune, coagulative, complement-mediated, and cytokine-driven systems, have been implicated in chronic urticaria. Autoimmunity has lately been suggested as having a significant impact in chronic urticaria. Numerous autoimmune disorders, including Type 1 diabetes, rheumatoid arthritis, Sjogren syndrome, celiac disease, and others, have been found to cluster in people with urticaria, providing more evidence for the autoimmune origins of chronic urticaria[32].

The most prevalent autoimmune conditions that accompanied CU patients were thyroid disorders[29]. Endogenous histamine-releasing factors, particularly functional autoantibodies, are correlated with thyroid and perhaps other autoimmune diseases and have prognostic and therapeutic implications. Chronic stress and a minor underlying infection are typically seen in CSU patients[11].

A subset of individuals with CIU who have an autoimmune cause have a positive ASST, according to studies addressing this issue. Some of these patients' sera contain IgG anti-IgE, anti-Fc RI, or both autoantibodies, some of which can cause donor basophils or mast cells to release histamine[20]. IgG anti-IgE, anti-Fc RI, or both autoantibodies may be present in the sera of some of these patients, and some of these autoantibodies may trigger donor basophils or mast cells to release histamine. The majority of responders favor using second-generation antihistamines or corticosteroids as the initial UV treatment[19].

CONCLUSION

across conclusion, UV is a rare but difficult illness across all of the world. According to Witebsky's hypotheses, there is not enough evidence to classify chronic urticaria as an autoimmune illness, despite the fact that there is now strong evidence for the role of autoimmunity in the pathophysiology of a subgroup of people who have chronic spontaneous urticaria. About 50% of patients have positive "autoimmune" tests in vivo and/or in vitro, and there is a substantial quantity of circumstantial evidence indicating that chronic urticaria is an autoimmune illness. While there are still many unanswered questions regarding CSU, it is becoming more and more obvious that both autoimmunity (an IgG-mediated disease) and autoallergy (an IgE-mediated disease) can play a role in its pathogenesis and predispose individuals to the emergence of other autoimmune diseases. All CIU patients should undergo screening for thyroid autoimmunity and function to detect patients who need follow-up care or treatment for underlying thyroid dysfunction at an early stage.

REFERENCES

1. Chronic urticaria-assessment and treatment clinical [Internet]. Available from: www.ascia.org.au.
2. Sadowska-Przytocka A, Czarnecka-Operacz M, Łącka K, Jenerowicz D. Autoimmune urticaria. Central-European Journal of Immunology. Termedia Publishing House Ltd.; 2013;38:265–70.
3. Marsland AM. Autoimmunity and Complement in the Pathogenesis of Chronic Urticaria. 2006.
4. Juan Tong L, Balakrishnan G, Kochan JP, Kin JP, Kaplan AP, Brook S. Assessment of autoimmunity in patients with chronic urticaria. J Allergy Clin Immnnol. 1997;99:1-6.
5. The Role of Infection and Autoimmunity in Urticaria and Angioedema as a Common Entity. 2019.
6. Jáuregui I, Ortiz De Frutos FJ, Ferrer M, Giménez-Arnau A, Sastre J, Bartra J, et al. Assessment of Severity and Quality of Life in Chronic Urticaria. Vol. 24, J Investig Allergol Clin Immunol. 2014.
7. Jáuregui I, Ortiz De Frutos FJ, Ferrer M, Giménez-Arnau A, Sastre J, Bartra J, et al. Assessment of Severity and Quality of Life in Chronic Urticaria. Vol. 24, J Investig Allergol Clin Immunol. 2014.
8. Wedi B, Raap U, Wieczorek D, Kapp A. Urticaria and infections. Allergy, Asthma & Clinical Immunology. 2009 Dec;5(1):33-36.
9. Lapolla W, Desai N, English JC. Clinical utility of testing for autoimmunity in chronic idiopathic urticaria. J Am Acad Dermatol. 2012 Mar;66(3):50-55.

10. Mortureux P, Leaute-Labreze C, Legrain-Lifermann V, et al. Acute urticaria in infancy and early childhood: a prospective study. Arch Dermatol 1998;134:319–3.
11. Bansal CJ, Bansal AS. Stress, pseudoallergens, autoimmunity, infection and inflammation in chronic spontaneous urticaria. Vol. 15, Allergy, Asthma and Clinical Immunology. BioMed Central Ltd.; 2019.
12. Abd El-Azim M, El-Azim A. Chronic Autoimmune Urticaria: Frequency and Association With Immunological Markers. Vol. 21, Immunological Markers J Investig Allergol Clin Immunol. 2011.
13. Schoepke N, Asero R, Ellrich A, Ferrer M, Gimenez-Arnau A, E. H. Grattan C, et al. Biomarkers and clinical characteristics of autoimmune chronic spontaneous urticaria: Results of the PURIST Study. Allergy: European Journal of Allergy and Clinical Immunology. 2019 Dec 1;74(12):2427–36.
14. Murdaca G, Paladin F, Borro M, Ricciardi L, Gangemi S. Prevalence of Autoimmune and Autoinflammatory Diseases in Chronic Urticaria: Pathogenetic, Diagnostic and Therapeutic Implications. Biomedicines. MDPI; 2023;11:70-76.
15. Gu SL, Jorizzo JL. Urticarial vasculitis. Vol. 7, International Journal of Women's Dermatology. Elsevier Inc.; 2021. p. 290–7.
16. Kaplan A. Chronic urticaria: *pathogenesis and treatment*. J Allergy Clin Immunol 2004; 114: 465–74.
17. Rottem M. Chronic urticaria and autoimmune thyroid disease: is there a link? Vol. 2, Autoimmunity Reviews. 2003.
18. Kulthanan K, Cheepsomsong M, Jiamton S. Urticarial Vasculitis: Etiologies and Clinical Course. Vol. 27, ASIAN PACIFIC JOURNAL OF ALLERGY AND IMMUNOLOGY. 2009.
19. Kolkhir P, Bonnekoh H, Kocatürk E, Hide M, Metz M, Sánchez-Borges M, et al. Management of urticarial vasculitis: A worldwide physician perspective. World Allergy Organization Journal. 2020 Mar 1;13(3):18-25.
20. Napoli DC, Freeman TM. Autoimmunity in Chronic Urticaria and Urticarial Vasculitis. Curr Allergy Asthma Rep. 2001;1:329–36.
21. Wanxiang S, Xiaoming L, Khalaf AT, Jiquan S, Jinquan T. Relation between Autoimmunity Chronic Urticaria and the Levels of Plasma Prothrombin F 1+2. Am J Appl Sci. 2007;4(12):965–9.
22. Grattan C. The urticarias: pathophysiology and management. Clin Med (Lond). 2012 Apr;12(2):164-7. doi: 10.7861/clinmedicine.12-2-164. PMID: 22586795; PMCID: PMC4954105.
23. Asero R, Riboldi P, Tedeschi A, Cugno M, Meroni P. Chronic urticaria: A disease at a crossroad between autoimmunity and coagulation. Vol. 7, Autoimmunity Reviews. 2007. p. 71–6.
24. Philpott H, Kette F, Hissaria P, Gillis D, Smith W. Chronic urticaria: The autoimmune paradigm. Vol. 38, Internal Medicine Journal. 2008. p. 852–7.
25. Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: What we know and what we do not know. Journal of Allergy and Clinical Immunology. 2017 Jun 1;139(6):1772-1781.e1.
26. Chiu HY, Muo CH, Sung FC, Fung-Chang Sung C. Associations of chronic urticaria with atopic and autoimmune comorbidities: a nationwide population-based study.
27. Caproni M, Volpi W, Giomi B, Cardinali C, Antiga E, Melani L, et al. Chronic idiopathic and chronic autoimmune urticaria: Clinical and immunopathological features of 68 subjects. Acta Derm Venereol. 2004;84(4):288–90.
28. Stitt JM, Dreskin SC. Urticaria and autoimmunity: Where are we now? Curr Allergy Asthma Rep. 2013 Oct;13(5):555–62.
29. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: Associations found in a large population study. Journal of Allergy and Clinical Immunology. 2012 May;129(5):1307–13.
30. Kikuchi Y, Kaplan AP. Mechanisms of autoimmune activation of basophils in chronic urticaria. Journal of Allergy and Clinical Immunology. 2001;107(6):1056–62.
31. Kolkhir P, Altrichter S, Asero R, Daschner A, Ferrer M, Giménez-Arnau A, et al. Autoimmune Diseases Are Linked to Type IIb Autoimmune Chronic Spontaneous Urticaria. Allergy Asthma Immunol Res. 2021;13(4):545-8.
32. Gold-Olufadi S, Ayanlowo O, Akinkugbe A, Otrofanowei E. Chronic urticaria in blacks: Is autoimmunity an important etiological factor? Nigerian Journal of Medicine. 2022;31(1):82-9.

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