REVIEW ARTICLE

Chronic spontaneous urticaria: An updated comprehensive review of etiology, pathogenesis and management

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ABSTRACT

Chronic spontaneous urticaria (CSU) is characterized by spontaneous occurrence of wheals without an obvious stimulus that lasts for most days of week for more than 6 weeks. It is the most common subtype of chronic urticaria, with point prevalence between 0.5% and 1%.

The exact etiopathogenesis of CSU remains poorly understood. Some of the possible causes of CSU include acute or chronic infections, pseudo allergies to food and drugs, allergic reactions to medications, insect bites and stings, and autoimmunity including autoimmune thyroid disorders. There is significant evidence of functional IgG autoantibodies directed against IgE or the high-affinity IgE receptor in 25-30% of patients in CSU. In around half the cases of CSU, even after exhaustive panel of investigations, the cause may still remain elusive. Nevertheless, some characteristic lab findings may help to point towards the possible cause. Like, increased ESR suggests the possibility of an underlying systemic disease or infection, whereas, eosinophilia should prompt search for any parasitic infection. Similarly, screening test for thyroid function along with anti-TPO and anti-TG levels when done in appropriate cases, can at times yield a positive result.

Clinically, it is characterized by presence of evanescent wheals with or without angioedema. While wheals are erythematous, completely blanchable evanescent plaques of various sizes, angioedema is result of dermal and subcutaneous edema. The wheals are associated with itching and occasionally burning sensation. They are migratory in nature. Angioedema is present in 40-50% of cases.

Preferred first line treatment of CSU are newer generation H1 antihistamines. These include cetirizine, loratadine, desloratadine, fexofenadine and mizolastine. However, in pregnancy, chlorpheniramine and diphenhydramine are preferred oral and intravenous antihistamines respectively. In case of no response, the dose can be raised up to four times the standard doses. Short course oral corticosteroids like prednisolone in the dose of 0.3-0.5 mg/kg, tapered over 4-6 weeks can be given in recalcitrant cases. Leukotriene receptor antagonist, Zafirleukast in dose of 20 mg twice daily and Monteleukast in dose of 10 mg once a day have shown superior efficacy in patients with urticaria aggravated by pseudoallergens. Biologic agents like omalizumab have also shown promising results in resistant cases of CSU, not controlled by any other drugs.

KEY WORDS: Chronic spontaneous urticaria, Etiology, Treatment

INTRODUCTION

Chronic spontaneous urticaria (CSU) is characterized by spontaneous occurrence of wheals without an obvious stimulus that lasts for most days of week for more than 6 weeks.[1,2] A point prevalence between 0.5% and 1% for CSU has been proposed.[3]

CSU is the most common subtype of chronic urticaria.[4] The long lasting course and distressing symptoms have great impact on quality of life. The exact etiopathogenesis of CSU remains poorly understood. Possible causes of CSU in-

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clude acute or chronic infections, pseudo allergies to food and drugs, allergic reactions to medications, insect bites and stings, and autoimmunity including autoimmune thyroid disorders.[5] There is increasing evidence that inflammation and unbalanced immunity play critical roles in generation and promotion of symptoms.[6-10] Immunoglobulin(Ig) E mediated allergy is probably never the cause of CSU, except in rare event that unrecognized food allergy in very young children might present with recurrent weals over a period of weeks until the cause is suspected and withdrawn.[11]

Strong link has been reported between CSU and elevated levels of IgG antithyroid antibodies,[12] with large number of studies reporting positivity varying from 20.4% to 57.6%, of IgG against thyroid peroxidase (TPO) and 15.2% to 42.5% of IgG against thyroglobulin (TG).[13,14] Levels of IgG anti thyroid antibodies are more often elevated in adults with CSU than in children and in females more than males.[15]

An autoimmune etiology characterized by the presence of histamine releasing autoantibodies directed against the subunit of high affinity IgE receptor (FcεRI) or IgE has been found in approximately 35-45% of CSU patients.[16] These autoantibodies can be detected by Autologous Serum Skin Test (ASST).[17] The sensitivity and specificity of ASST for autoantibody detection in patients of CSU is reported to be 80% at best compared with the in vitro basophil histamine release assay.[18] ASST is an in vivo screening test for detecting histamine releasing autoantibodies and has a high negative predictive value.[19,20] Antibodies against FcεRI and IgE are detectable only in a third of patients with CSU, suggesting that other circulating mediators, including cytokines may be involved in the pathophysiology.

One very important proposed association of CSU is with contact allergic sensitization. It has been seen that patients with CSU without a detectable underlying etiologic factor, can have positive patch test results and avoidance of the sensitizing substance can be effective in remission of symptoms. Patch test positivity in patients with CSU have been reported to vary between 42.9% to 96%.[21,22] Thus patch testing is a very feasible and easy to perform procedure which has been evaluated earlier but has not been included in standard guidelines for diagnosis.

Most allergic and autoimmune diseases are caused by an imbalance between cytokines and T lymphocyte subgroups. The activity of T cells is largely dependent on differentiation of T0 cells into subtypes of CD4+ T helper (Th) cells, such as Th1, Th2, Th17 and Th22 cells which can be further grouped based on distinct cytokine profiles.[23] While Th1 cytokines like Interferon-gamma(IFN-γ), Interleukin(IL)-2 and Tumor Necrosis Factor(TNF)-α are involved in pro-inflammatory responses, Th2 cytokines like IL-4, IL-5, IL-6 and IL-10 can inhibit Th1 cytokine production inhibition, augment humoral responses, and mediate allergic diseases.[24] The imbalance between Th1 and Th2 cytokines has long been proposed as a possible mechanism in urticaria.[25,26]

Majority of research works and studies in etiology of CSU have focussed on a single parameter. Contact allergic sensitization had not been studied much. Association between various etiological factors such as contact sensitization, autoreactivity and antithyroid antibodies with cytokines like IL-6 and IFN-γ had either not been studied previously or meagre literature was

available for the same. Therefore we planned to study various etiological factors in CSU and their association with IL-6 and IFN γ. Chronic urticaria is defined as the repeated occurrence of daily or almost daily cutaneous wheals accompanied by redness and itching for more than 6 weeks.[27] It is characterized by presence of wheals and angioedema. While wheals are due to swelling in superficial dermis, angioedema is because of swelling of deep dermis and subcutaneous tissue or submucosa.[27]

Patients suffering from chronic urticaria are considerably more difficult to satisfy and treat and have a bigger emotional burden than the average patient in dermatology.[28] It is difficult to establish a cause and is very often impossible to ascertain the triggering factor.

Etiology of chronic idiopathic urticaria (CIU) or CSU has been a matter of debate and several researches have been done to potentiate the cause. Contact sensitization, autoimmunity and defects in balance between various cytokines have been proposed as potential etiopathogenic factors. However the laboratory investigations are not always conclusive and only can be suggestive of underlying etiology.[12]

EPIDEMIOLOGY

About 15 to 20% of the general population is expected to suffer from urticaria at least once during their lifetime.[27] The highest incidence occurs in young adults with most of the patients experiencing their first episode in adolescence.[27] It is twice as common in women as men.[27] There are multiple etiological factors in causation of chronic urticaria. In a study conducted by Singh et al.[29] out of 500 patients of chronic urticaria, 37% suffered from physical urticarias.

ETIOLOGY

There is a long list of both internal as well as external factors that can trigger development of wheals with or without angioedema. In a gist, they can be physical, autoimmune, idiopathic, vasculitic, pseudoallergic and infectious, with idiopathic being the most common.[12]

Idiopathic: Most cases of chronic urticaria are idiopathic. It has been proposed that autoimmunity may play an important role in causation of CSU.[30, 31] Most common offenders include:

Medicines: Urticaria can be exacerbated by a number of drugs. Most common drugs include aspirin, other non-steroidal anti inflammatory drugs, opioids, ACE inhibitors and alcohol.[32] Aspirin may exacerbate the disease in as many as 6.7%-67% of the cases.[33-35]

Contactants: Development of urticarial wheals within 30-60 minutes of contact with offending agent is called as contact urticaria.[12] Precipitating factors include latex, plants and animals like caterpillars, dander and medications.[12]

Neurological: It was found in an Italian study, that urticaria may be associated with fibromyalgia, for which fibromyalgia-neurogenic skin inflammation was put forth as pathogenic mechanism.[36]

Stress: Psychological stress may be associated with aggravation of chronic urticaria in a number of patients. Depression has been found to cause as well as worsen chronic urticaria.[37]

AUTOIMMUNITY

Grattan and co-workers, about 3 decades ago, demonstrated that autologous serum injected intradermally led to development of wheal and flare reaction in many patients of chronic urticaria, which led to the conclusion that there may

be presence of histamine releasing factor in the blood. This led to the concept of chronic urticaria due to autoimmunity and autologous serum skin test became a part of armamentarium to diagnose autoimmune urticaria.[38] However ASST may be positive in some cases of cold induced physical urticarias as well.[39]

Anti IgE antibodies were found in patients of chronic urticaria and this was proposed to be cause of autoimmunity.[40] However, it is now well-established that about 30-50% patients with chronic urticaria have circulating functional auto antibodies against the high-affinity IgE receptor (FCeRIa) or against IgE. Urticaria has also been seen associated with some autoimmune diseases.[41] To enumerate a few, systemic lupus erythematosus, cryoglobulinemia, neoplasms, juvenile rheumatoid arthritis and autoimmune thyroid disease, including Graves disease.[42]

At least 1/3rd of patients with CSU, ranging from 25 to 60%, have circulating functional autoantibodies against high affinity IgE receptor or less commonly IgE itself, the presence of which can lead to positive ASST.[43] In an attempt to demonstrate presence of auto antibodies in patients with CSU, Safari M et al.[44] performed a cross sectional study by subjecting 38 patients (25 females and 13 males) to ASST. In 15 patients (39%), ASST was positive of which 10 were females (67%).

Hundred and eleven CSU patients were enrolled by Kumar Y H K et al.[45] to study positivity of ASST. It was found that 43.62% patients had ASST positivity with statistically significant increased numbers of angioedema episodes.

Sharkawy R E et al.[46] performed ASST, Urticaria severity score (USS) and serum levels of anti IgE receptor antibodies in 108 of chronic urticaria. ASST was positive in 38% patients with statistically significant relationship between positivity and duration of disease. Also, severity of disease, as measured by USS was statistically significant in relation to positive ASST. Of the patients who had positive anti IgE levels, 90.9% had positive ASST and the mean of antibodies in these patients was higher than the ones with negative ASST.

Al-Hamamy HR et al.[47] included 54 patients of chronic urticaria and subjected them to ASST. Twenty-two of these patients were ASST positive, 15 females and 7 males. Only significant association in positive group was predominance of lesions on face and extremities as compared to the negative group. There was no significant association of positive ASST with disease duration, presence of angioedema, positive family history of urticaria, atopy or autoimmune diseases.

Aktar S et al.48 performed ASST and APST in 50 patients of chronic or recurrent urticaria. While ASST was positive in 23 patients, APST was positive in 36 patients. It was found that APST was positive in 48% patients with negative ASST, however all patients with negative APST also were negative for ASST. Both the tests were statistically significantly positive in old patients, although no correlation with positive tests and disease severity were found.

PSEUDOALLERGIC

Pseudoallergic reaction means implication of a drug or food product that clinically presents as an allergic reaction but there are no specific IgE antibodies to the offender in blood. Some authors believe psuedoallergy to be a culprit in causation of CSU. However the incidence of CSU due to specific foods may vary between 2 to 30%.[49]

Implicated agents include, sweeteners, artificial food dyes, preservatives, aromatic volatile compounds in tomatoes, herbs, wine, salicylic acid, orange oil, alcohol and high dietary fats. Some patients report the onset of acute urticaria associated with the consumption of certain foods, such as shellfish, eggs, nuts, strawberries or certain baked goods. This type of chronic urticaria is more common in infants and children.[50]

Food induced chronic urticaria was studied by Chung BY et al.[51] and it was found that only few of the patients who claimed to have urticarial symptoms after consuming particular food products had positive results after being subjected to oral food challenge. However, in a study carried out by Akoglu et al.[52] in 34 patients of CSU who were put on a low pseudoallergen diet, 14 patients (41.2%) showed improvement in the symptoms.

Son J H et al.[53] evaluated the role of histamine in food in causation of CSU and whether histamine-free diet had any positive impact on reduction of symptoms and severity of urticaria symptoms. They enrolled 22 CSU patients, who were on histamine uncontrolled diet before start of the study. Plasma diamine oxidase (DAO) levels were evaluated before and after dietary restrictions. Dietary products like tuna, mackerel, fermented cabbage and radish, mayonnaise, yogurt, cheese, ketchup, wine, beer, grapes, bananas and strawberries were restricted. Also, severity of symptoms was recorded by using UAS and USS. It was found that the severity of the disease declined after diet restriction for 4 weeks. There was a statistically significant reduction in the levels of plasmas histamine and DAO activity.

In an attempt to evaluate role of food as trigger of CSU, Sanchez J et al.[54] recruited 245 patients of CSU and 127 healthy controls. The patients and controls filled a questionnaire regarding triggering food products and were subjected to challenge test, skin prick test (SPT) and specific IgE measurement by immunofluorescence. It was found that asthma and IgE sensitization were significantly higher in patients than controls. About 66% patients and 24% controls self reported at least one reaction with some food. Nearly 40% CSU patients reported at least 2 food products triggering their symptoms. There were, however, no significant differences in SPT and serum IgE levels for any food. Only 1.2% patients had positive challenge test, thereby concluding that food is an uncommon trigger for CSU.

Magerl M et al.[55] recruited 140 moderate to severe patients of CSU who responded inadequately to treatment and subjected them to pseudoallergen diet for 3 weeks. Severity of disease was recorded using UAS4. Use of drugs like corticosteroids and anti-histamines was allowed but was recorded and analyzed. They found 20 patients to be strong responders to diet restriction, 19 patients to be partial responders and 9 patients reported substantial reduction in their medication without worsening of their symptoms. They concluded that pseudoallergen diet is safe and healthy measure to identify CSU patients whose symptoms can improve with dietary measures.

Similarly, Wagner N et al.[56] recruited 56 CSU patients and subjected them to low-histamine diet for 3 weeks. UAS was used to measure severity of symptoms and Diamine oxidase (DO) levels were measured before giving the diet. 34 patients showed statistically significant decrease in severity and improvement in quality of life after taking the diet. However, DO levels remained stable.

Siebenhaar F57 recruited a cohort of 157 patients of CSU with a UAS7 score of more than or equal to 10 and subjected them to detailed history regarding development of symptoms after consuming histamine rich foods. Subsequently these patients were subjected to histamine low diet to look for improvement of symptoms and also to a 75 mg oral histamine challenge test. It was found that 34% gave positive history of exacerbation of whealing on consuming offending food. About 46% showed improvement in UAS7 score by 7 or more post restriction diet and 17% developed whealing response to histamine provocation. There was very little correlation between history positivity, diet restriction improvement positivity and histamine provocation test positivity. Similar proportion of diet and histamine provocation patients gave positive history of lesions to histamine rich food; similar proportion of history positive and negative patients developed improvement on dietary restrictions and similar proportions of patients gave positive history of whealing amongst positive provocation group. Overall, only 2 patients were common in all three groups.

INFECTIONS

Many infectious agents may be associated with development of urticaria. However these associations may be spurious, as they are not strongly validated. Infectious agents reported to cause urticaria include hepatitis B virus, *Streptococcus* and *Mycoplasma* species, *Helicobacter pylori*, *Mycobacterium tuberculosis*, and *herpes simplex* virus.[58,59] Not only bacterial and viral agents, but fungal and parasitic agents may also be implicated, namely candidiasis, onychomycosis, tinea pedis, strongyloidiasis, giardiasis and amoebiasis.[60,61]

Wedi B et al.[36] systematically reviewed existing studies addressing the effect of antibiotic therapy for chronic urticaria patients infected with *H.pylori*, they found that resolution of urticaria was more likely when antibiotic therapy was successful in eradication of *H.pylori*.[62] Apart from *H.pylori*, and other bacterial, viral or fungal infections like streptococci, staphylococci, Yersinia, giardia, mycoplasma, hepatitis virus, norovirus, parvovirus B19, Anisakis simplex, Entamoeba spp., Blastocytosi spp. have been implicated to be underlying causes of CSU.[4]

Celin Z et al.[63] presented a case series of 4 patients of chronic urticaria who sought help at their allergy clinic in Alfred Health, Melbourne. The patients were immigrants from Vietnam, India, Fiji and Japan and had symptom duration ranging from 6 months to 5 years. They all had positive evidence of Strongyloides infection and their symptoms of whealing improved after successful treatment of intestinal infection with oral ivermectin, thus emphasizing role of infections in causation of urticaria.

Lehloenya R and Christian S64 published a case report of a 51 years old female suffering from chronic urticaria of unknown cause for 5 years which was complicated intermittently by symptoms of urinary tract infection. Her urine sample was subjected to culture and microscopy, which grew *Raoultella ornithinolitica* in 3 days. She was treated for urinary tract infection with ofloxacin with complete resolution of urticaria symptoms.

Richard Evans[65] undertook a study of records of 100 patients of chronic urticaria referred to dental department for evaluation. He found that 35 patients had chronic dental abscess, advanced

periodontal disease was diagnosed in 28 patients and both alveolar abscess and periodontal disease were present in 13 patients. Fifty patients had no evidence of dental infection. Of the 50 affected patients, 17 were treated and were followed up. While in 11 patients, treatment of dental infections had no effect on course of urticaria, 6 patients showed relief of symptoms of urticaria following dental surgery and symptoms remained absent in follow up period of 1 month to 13 years.

Jhamnani R et al.[66] published case report of 2 females with chronic urticaria and signs of infection. The first patient was 39 year old female with chronic urticaria and symptoms of diarrhea and vomiting, while the second patient was a 36 year old female with chronic urticaria of 6 months duration and history of angioedema along with history of aggravation of symptoms after sexual activity. While the stool culture of the first patient was positive for *Giardia lamblia*, the second patient was diagnosed to have *Trichomonas vaginalis* infection. Both patients were treated with metronidazole and reported resolution of their urticarial symptoms.

CONTACT SENSITIZATION

One very important proposed association of CSU is with contact allergic sensitization. It has been seen that patients with CSU without a detectable underlying etiologic factor, can have positive patch test results and avoidance of the sensitizing substance can be effective in remission of symptoms. Patch test positivity in patients with CSU have been reported to vary between 42.9% to 96%.[21,22]

Patch testing is an effective procedure to diagnose contact sensitivity in patients of CSU in whom no underlying cause has been found. In a study, 23 patients were eligible to study role of contact allergens. Eligibility criteria for the study included (1) documentation of hives by a referring physician and/or symptoms of evanescent skin swellings for at least 6 weeks and (2) ability to come in for at least 3 clinical visits (patch test placement and 2 follow-up visits for reading). On an average 147 allergens were tested per patient. All patients were tested to a modified North American Contact Dermatitis Group (NACDG) series and cosmetic and fragrance series. Other series were placed, based on history, physical examination, and occupational exposures. Of the 23 patients, 22 (96%) had at least 1 positive patch test reaction of 1+ or stronger, whereas 9 patients (39%) had at least 1 positive reaction of 2+ or stronger. The most common allergen was potassium dichromate (n=9), and other positive allergens included nickel sulphate, cobalt chloride, neomycin and p-phenylenediamine.[21]

In another study conducted by Hao Chen et al.[22] 543 CSU patients were patch tested with European baseline series (IQ Chamber System, Sweden). Two hundred and thirty-three patients (42.9%) had positive reactions to the contact allergens. Among these patients, 146 (62.66%) had a positive reaction to 1 allergen, 55 (23.61%) to 2 allergens, 21 (9.01%) to 3 allergens, 6 (2.58%) to 4 allergens, and only 5 (2.14%) to 5 or more allergens. Potassium dichromate was the most common sensitizer (10.5%, n=57). Carba mix, nickel sulphate, fragrance mix, formaldehyde and cobalt chloride were other positive allergens in the series.

Khalid M. Alghamdi et al.[67] evaluated patch test reactivities in 93 patients with CSU. Approximately half of the patients (50/93) experienced

severe symptoms of urticaria, but only 26.9% (25/93) had graded their urticaria as very severe. Patients were also subjected to SPT. Negative results from SPT were reported in 62.4% (58/93) of patients and were subsequently patch tested. These patients also had no other etiologic factors (eg, infection; thyroid, autoimmune, or metabolic disease). Of the 58 patients of CIU who were patch tested, 31 (53.4%) had positive results. Positive allergens included nickel, cobalt, potassium dichromate, formaldehyde, fragrance mix, thiomersal.

Fifty-seven CU patients were subjected to patch testing by Sharma AD et al.[68] after exclusion of physical urticarias. Indian standard series was used. Eleven patients showed positive patch test results and were asked to avoid the incriminating allergen. Nine patients showed improvement with complete disappearance of symptoms within 2-3 weeks of avoidance. Most common allergens were metals.

SYSTEMIC DISEASES

Many rheumatic disorders, autoimmune disorders like thyroiditis and neoplasms may be responsible for urticarial wheals. While connective tissue disorders usually present with urticarial vasculitic features, they may rarely also present with classical urticaria. While both hyperthyroidism i.e Grave's disease and hypothyroidism i.e Hashimoto's disease may have urticaria as one of the cutaneous manifestations, patients are usually euthyroid.[69,70]

Thyroid autoimmunity has been thought to be a common comorbidity in patients of CSU in various studies.[13,14] A case control study to find prevalence of thyroid autoimmunity i.e prevalence of anti-TPO antibodies and anti-TG antibodies in Spanish people with chronic urticaria included 343 CSU patients and 282 age and sex matched healthy controls. The frequency of anti-thyroid autoantibodies in patients with CIU was 26.8% (n = 92) compared to 2.5% (n = 7) in healthy controls ($p< 0.001$). Pathological levels of anti-TPO (>90 IU/mL) were detected in 70 (20.4%) patients and in 5 (1.8%) healthy controls ($p< 0.001$). Elevated anti-TG titers (>70 IU/mL) were present in 52 (15.2%) patients and in 3 (1.1%) controls ($p< 0.001$).[13]

Sugiyama et al.[71] investigated the frequency of Hashimoto's Disease (HD) as a comorbidity of CSU and the prevalence rate of autoreactivity among CSU patients with HD. The presence of thyroid autoantibodies and the levels of thyroid hormones were examined in 40 CSU patients who showed urticaria symptoms for >4 weeks. Patients who were diagnosed with HD, including subclinical ones, and were in need of treatment, received thyroid therapy, and the changes in their urticarial symptoms were observed. An ASST was also performed in 13 out of 40 patients, who gave consent to examine the relation of CSU with autoreactivity. Eleven of the 40 CSU patients were diagnosed with HD (5 were positive for anti TG antibodies, 3 for anti TPO antibodies and 3 for both). Seven of these 11 were given thyroid therapy and 5 completed the therapeutic regimen. Four of these 5 patients showed considerable remission of urticarial symptoms during and after treatment. In addition, the rate of positive ASST results tended to be higher in CSU patients with HD than in those without HD. A case control study performed in Karachi recruited 90 subjects that were divided into 3 groups: Group1 had 30 patients with diagnosed CSU, Group 2 had 30 patients diagnosed with

hypothyroidism and Group 3 had 30 age and sex matched healthy controls. Elevated titers of anti TG antibodies were found to be positive in 9 (30%) patients in group 1 and 24 (80%) patients in group 2 compared to the controls ($p < 0.001$). Elevated titers of antimicrosomal autoantibodies were detected in 13 (43.3%) patients in group 1 and 27 (90%) patients in group 2 with hypothyroidism compared to the control group ($p < 0.001$). Among 30 patients with diagnosis of hypothyroidism, 17 (56.7%) were found to have chronic urticaria compared to age matched healthy controls. Among 30 cases of chronic urticaria, 3 (10%) were found to be hypothyroid compared to age and sex matched healthy controls. Out of a total 47 patients with chronic urticaria with or without hypothyroidism, elevated titers of anti TG antibodies and anti TPO antibodies were found to be positive in 42.5% and 57.6% patients, respectively.[14]

To study the association of thyroid autoimmunity in children and adolescents with chronic urticaria, 187 patients were referred for evaluation of chronic urticaria during a 7.5 year period. Eight (4.3%) females, aged 7–17 years had increased levels of antithyroid antibody, either anti TPO antibody (n = 4, >75 IU/ml), anti TG antibody (n = 2, >150 IU/ml) or both (n = 2).[72]

In a retrospective study of 1096 patients of chronic urticaria by Komurtnart C et al.[73] 60.2% patients had CSU. They were studied in detail, especially with respect to their thyroid profiles and responses to ASST and autologous plasma skin test (APST). It was found that anti-thyroid antibody positivity was more common in female gender and age >35 years. Also, the patients who tested positive to anti-TPO antibodies had longer duration of disease activity i.e longer than 12-18 months compared to the ones who tested negative for the same. The patients who responded positively to ASST and APST had more frequent episodes of whealing i.e >4/ week compared to the ones who responded negatively. Also ASST and APST positive patients were found to be more resistant to therapy than the negative group.

Kim S Y et al.[74] conducted a population based study to evaluate the risk CSU in patients with autoimmune thyroid disease (AITD) and also other demographic risk factors associated with CSU. In this study, 3659 AITD patients and 18295 controls were enrolled. It was found that AITD patients had a significantly higher tendency to develop CSU, compared to the controls, with patients with Hashimoto's disease being more prone than Grave's disease, however statistically insignificantly. Also, patients with type 2 diabetes mellitus, hypertension, dyslipidemias, allergic rhinitis, atopic dermatitis and asthma had higher risk of developing CSU.

One hundred and forty eight patients and age-sex matched controls were included in a study by Magdalena C O et al.[75] to study relationship between deranged thyroid profiles in patients of chronic urticaria and to find link between chronic urticaria and AITD. Statistically significant difference was found between levels of free T3 and anti-TG between patients and controls while levels of free T4, anti-TPO and thyroid stimulating hormone were comparable. Also, treatment with levothyroxine did not improve skin disease.

To substantiate the role of thyroid autoimmunity in patients of chronic urticarias, Halilovac E K et al.[76] involved 70 patients and controls and found that 22.85% and 30% was the positivity for anti-TPO and anti-TG in patients which was statistically higher than the controls.

To establish causality between anti-TPO IgE and chronic urticaria, Sanchez J et al.[77] took 3 groups of patients, namely- ones with CSU, healthy controls and patients with AITD. All the study subjects were subjected to evaluation of serum anti-TPO IgE, anti-TPO IgG and basophil activation test by measuring CD203c, ASST and SPT. It was found that CSU group of patients has higher prevalence of atopy and total IgE than other 2 groups. Positive ASST was statistically significantly higher in CSU patient group than other 2 groups. Anti-TPO IgE was positive in 34% of CSU patients, 16.6% of AITD patients and 8.1% controls, which was statistically significant. However anti TPO IgG was higher in AITD group compared to CSU patients, who had higher levels than that of controls. Higher expression of CD203c was observed in patients of CSU although total basophil concentration was lower than controls and AITD patients.

DRUGS

Aspirin and other non-steroidal anti inflammatory drugs like diclofenac can lead to aggravation of urticaria by non-allergic mechanisms.[78] Percentage of patients whose symptoms of urticaria were exacerbated by aspirin varied from 20% to 30% in different studies.[35,79] Drugs usually cause acute urticaria by IgE mediated mechanisms but some drugs, such as opiates or codeine, act directly on mast cells, and others such as aspirin and other nonsteroidal anti-inflammatory drugs, induce an exacerbation of chronic urticaria by a pharmacological mechanism involving the arachidonic acid metabolism. Additionally, angioedema is a well-known complication of angiotensin-converting enzyme inhibitors by its action on bradykinin.[80]

Sanchez J et al.[81] included 245 CSU patients and 127 healthy subjects to estimate the impact of the drugs in exacerbations of CSU. About 37.5% patients and 23.6% subjects in the control group reported at least one drug reaction with drugs non steroidal anti-inflammatory drugs (NSAIDS) and beta lactams. However only 13% in patient group showed positive drug challenge test.

Cavkaytor O[82] enrolled 81 children with chronic urticaria to ascertain implication of aspirin hypersensitivity. Children with more than 4 episodes of urticaria /week were classified into chronic persistent urticaria (CPU) while the ones who suffered from 2-4 episodes/week were classified into chronic recurrent urticaria (CRU). Children were subjected to single blind, placebo controlled aspirin provocation tests and it was found that 24% of children with CPU and 10% of children with CRU had positive provocation test.

Rajan JP[83] recruited 100 patients of CSU to study prevalence of sensitivity to drug and food additives in patients of CSU. Forty-three of these patients gave positive history of allergy to drug or food additives. These 100 patients were subjected to single blind provocation with 11 drug and food additives, namely-tartrazine (FD&C Yellow 5), monosodium glutamate, potassium metabisulfite, aspartame, methyl paraben, sodium benzoate, butylated hydroxy anisole, FD&C Yellow 6, butylated hydroxy toluene, sodium nitrite and sodium nitrate. Only 2 of these patients had positive test with urticarial whealing. These 2 patients were subjected to double blinded provocation with negative challenge result in both.

Doeglas HM et al.[84] subjected 131 patients of chronic urticaria, including both idiopathic as well as physical urticaria, to oral aspirin prov-

ocation test. Of these, 31 patients tested positive, which included 35% of chronic idiopathic urticaria, 52% of cholinergic urticaria patients and 43% of pressure urticaria patients. Patients testing positive were also tested with tartrazine, 4-hydroxy benzoic acid, sodium benzoate, sodium- and phenyl salicylate and the analgesics indomethacin, mefenamic acid and paracetamol. Nineteen out of 23 aspirin sensitive patients tested positive to one or more of these substances with highest positivity for indomethacin and tartrazine.

VASCULITIS

Urticarial vasculitis presents as generalized wheals or erythematous plaques, that may be associated with pain and burning sensation. In contrast to urticaria, they do not migrate and remain fixed for more than 24 hours. While the lesions may resemble urticaria clinically, histopathology shows presence of leukocytoclastic vasculitis.[85] Tsunemi et al.[86] reported a case presenting as annular urticarial plaques with eosinophilic vasculitis on histopathology.

MISCELLANEOUS

1. Grass pollens, mould, spores, animal dander, house dust and even tobacco smoke may provoke chronic urticaria.[87]
2. There may be worsening of urticaria premenstrually and also during pregnancy.[88]
3. Iatrogenic causes like metal pin in femur, metal dental prostheses, and with dental amalgams.[89,90]
4. Many dermatological conditions such as urticaria pigmentosa, dermatitis herpetiformis, pemphigoid etc may also produce urticaria-like lesions.[12]

PATHOGENESIS

Urticaria is mast cell centered disease, which can be degranulated by a number of immunological and non-immunological stimuli. Type I allergy seen in acute urticaria, mediated by cross-linking of mast cell bound specific IgE to the exogenous allergens, is rarely implicated in CSU. Another mechanism of causation of acute urticaria, which is unimportant in CSU is binding of pathogen associated molecular patterns (PAMPs) on microbes to toll-like receptors on mast cells.

There is significant evidence of functional IgG autoantibodies directed against IgE or the high-affinity IgE receptor in 25-30% of patients in CSU. As a proof, it has been demonstrated that these autoantibodies can cause degranulation of healthy donor basophils and cutaneous mast cells in vitro and ex-vivo.[91-94] Complement component C5a is a co-factor in-vitro.[95] There is difference between the functionality of IgG autoantibody subclasses- IgG1 and IgG3 are closely related with histamine release from basophils, whereas IgG2 and IgG4 are not.[96]

The autoimmune hypothesis of CSU directly incriminates the functional autoantibodies in pathogenesis of CSU.[97] There is up regulation of activation markers on circulating basophils in a proportion of patient of CSU98 with reduced responsiveness to anti-IgE stimulation that appears to recover with spontaneous disease remission.[99] Although type I allergy is almost never implicated in CSU, IgE antibodies against self antigens such as TPO are found.[100]

Wheals and angioedema are the clinical manifestation of vasodilation and increased permeability of dermal and subcutaneous vasculature following release of both preformed as well as newly synthesized mediators from the mast cells.

While histamine is the major preformed mediator, prostaglandin D2 and platelet activating factor are newly synthesized. Adhesion molecules are upregulated under the influence of preformed TNF-alpha which lead to recruitment of neutrophils and eosinophils in the wheals. Basophils cause prolongation of wheal by releasing histamine after wheal initiation.[101] IL-6 and IL-8 were found to be increased in cold induced urticaria.102 Although role of T cells in unclear but Th0 cells predominate in lesional skin.[26] Also, increased vascular markers are expressed in lesional skin.[103] Different histamine receptor activation cause different manifestations. While H1 receptor causes symptoms of itch, flare, erythema and whealing, H2 receptor activation only causes erythema and flare and no itch or flare. H3 receptors, which act as inhibitory autoreceptors in central nervous system, have not been identified in human skin. Although H4 receptor activation leads to scratching behavior in mice,[104] a human equivalent has not been described. When compared to normal controls, cutaneous mast cells from patients of chronic urticaria release more histamine, not only spontaneously, but also under the influence of non-specific degranulating agents like codeine and morphine.[105] Reduction in dietary histamine metabolism by diamine oxidase in the bowel has been reported while there is no evidence of reduced cutaneous histamine degradation by N-methylhistamine.[106]

Most allergic and autoimmune diseases are caused by an imbalance between cytokines and T lymphocyte subgroups. Imbalance between Th1 and Th2 cytokines has been proposed to be a pathogenic mechanism in causation of chronic urticaria, which can be exemplified through many studies.

Th1 and Th2 interleukins have been found to be altered in patients of CSU. In a study to evaluate the cytokine pattern in CSU, 20 respective cytokines of Th1 (IL-1β, IFN-γ, granulocyte/macrophage colony-stimulating factor – GM-CSF, IL-2, IL-12p70, IL-28A, TNF-α, TNF-β), Th2 (IL-4, IL-5, IL-6, IL-10, IL-13, macrophage inflammatory protein-3a), Th17 (IL-17, IL-17F, IL-21, TGF-β, IL-23), and Th22 (IL-22) were measured in stored plasma using a commercially available multiplexed sandwich ELISA based quantitative array. ASST and SPT were performed. A total of 60 patients with CSU, including 15 ASST+/ SPT+, 15 ASST+/ SPT-, 15 ASST-/ SPT+, and 15 ASST-/ SPT-, were recruited. The plasma concentration of 11 cytokines were higher in the CSU than in the healthy control group, of which IFN γ (p= 0.004), IL-2 (p= 0.001) and IL-6 (p= 0.004) were most statistically significant. Thirty CSU patients were ASST+, and the other 30 were ASST-. The plasma level of 12 cytokines, including IL-2, IL-5, IL-6, IL-12p70, IL-13, IL-17, IL-21, IL-22, IL23, TGF-β1, TNF-α and TNF-β, was significantly higher in ASST+ CSU patients than in healthy controls. In ASST- CSU patients, only 5 cytokines were more significantly expressed, including IL-2, IL-6, IL-13, TGF-β1 and TNF-α. Of the 60 CSU patients, 30 were SPT+ and 30 were SPT-. Compared to healthy controls, 13 cytokines were significantly more abundant in the plasma of SPT+ CSU patients: IFN- γ, IL-2, IL-4, IL-5, IL-6, IL-12p70, IL-13, IL-21, IL-22, IL-23, TGF-β1, TNF-α and TNF-β. In SPT- CSU patients, only four cytokines, IL-2, IL-6, IL-21 and TNF-α, exhibited greater abundance. IFN-γ was significantly lower in ASST-/ SPT- than in ASST+/SPT+ (p = 0.0070), or than in ASST-/SPT+ (p = 0.0025) subgroups, whereas

IL-2 was significantly higher in ASST+/SPT+, ASST+/SPT-, and ASST-/SPT+ than in ASST-SPT- patients (p = 0.0079, 0.0251, and 0.0055, respectively).[107]

In another study, 100 patients with CIU and 200 matched healthy controls (HC) were chosen and on basis of high total serum IgE values (> 400), 30 subjects each from CIU and HC groups were selected for analysis of serum IFN-Y and IL-6. A significant increase was observed in mean serum levels of IFN-Y (80.762 – 62.056) and IL-6 (39.37 – 11.06) in patients compared to HC (24.79 – 21.84 and 7.175 – 4.81), respectively, at $p < 0.0001$.[108]

In another study IL-6 trans-signaling was studied in 58 CSU patients (18 men and 40 women; median age 38 years, range 24-52). Plasma concentration of IL-6 was significantly higher in CSU patients as compared with the healthy subjects (median: 3.32 vs. 0.69 pg/ml; $p<0.0001$). IL-6 plasma concentration was significantly higher in moderate-severe CSU patients as compared with those with mild CSU and the healthy subjects (median: 6.16 vs. 1.82 vs. 0.69 pg/ ml, $p<0.001$).[20]

Atwa MA et al.3 conducted study in 75 CSU patients and 30 controls to find association of CSU with levels of IL-17, IL-23 and TNF-α. They also aimed to study disease severity association with ASST positivity. They found that the levels of these cytokines were statistically significantly higher in patients than controls. Also, these cytokines showed higher measurable amounts in patients with positive ASST.

Degirmenci PB et al.[109] analyzed the association of levels of IL-4, IL-10, transforming growth factor β1 (TGF-β1), interferon-ϒ, IL-17A and IL-23 and CSU by ASST. Forty patients and 20 controls were enrolled. Twenty patients were ASST positive. All these cytokine levels were reduced in patients compared to the controls, with levels of IL-4 IFN-ϒ being less in patients with positive ASST than the ones with negative ASST. Severity of disease UAS was higher in ASST positive group.

Tao C et al.[110] recruited 40 patients of CSU, 30 patients of atopic dermatitis and 40 healthy controls to measure the levels of IL-35. Of the 40 cases of CSU, 20 were treated with H1 antihistamines. IL-35 levels were measured by using standard ELISA kits and it was found that the levels of IL-35 were significantly lower in CSU patients when compared to those of patients of atopic dermatitis and healthy controls. Also, it was found that after treatment with antihistamines in the 20 treated patients of CSU, the levels of IL-35 rose compared to baseline untreated levels.

CLINICAL FEATURES

CSU is characterized by presence of wheals with or without angioedema. While wheals are erythematous, completely blanchable plaques of various sizes, angioedema is result of dermal and subcutaneous edema. The wheals are associated with itching and occasionally burning sensation. They are migratory in nature. Angioedema is present in 40-50% of cases.[111]

The lesions may be localized or generalized, and may involve any part of the body including palms, soles and scalp. While wheals are very itchy, hardly any excoriations can be visualized on examination as the patient tends to rub the affected area instead of scratching it. Severe attacks of chronic urticaria may be accompanied by systemic features like headache, dizziness,

nausea, vomiting, shortness of breath, abdominal pain and hoarseness of voice.

Family or personal history of autoimmune diseases like thyroiditis may be a clue to chronic autoimmune urticaria, as otherwise no other distinctive features can be associated with it.[12] An assessment tool for scoring the severity of urticaria was proposed by a European panel on allergic diseases.[4]

Table 1 Severity score in urticaria[4]

SCORE	WHEALS	PRURITUS
0	None	None
1	Mild (<20 wheals/24 hours)	Mild
2	Moderate (21-50 wheals/24 hours)	Moderate
3	Intense (>50 wheals/24 hours) or large confluent areas	Intense

INVESTIGATIONS

Even after exhaustive investigations to ascertain the cause of chronic urticaria, about 50% of cases remain idiopathic.[113] Increased ESR should suggest possibility of an underlying systemic disease or infection, whereas, eosinophilia should prompt search for any parasitic infection. Screening test for thyroid function along with anti-TPO and anti-TG levels can be done.

Positive ASST can be indicative of autoimmune etiology.[114] In-vitro basophil histamine release assay is gold standard for quantifying autoantibodies.[115] In presence of only angioedema and C4 hypocomplementemia, hereditary angioedema can be suspected.[116] Investigations to rule out infective etiology like ASO, CRP, Hepatitis B and C serology should be carried out. The EAACI has given a diagnostic algorithm for chronic urticaria.[4]

British Society for Allergy and Clinical Immunology gave an algorithm for diagnosis of chronic urticaria.[112]

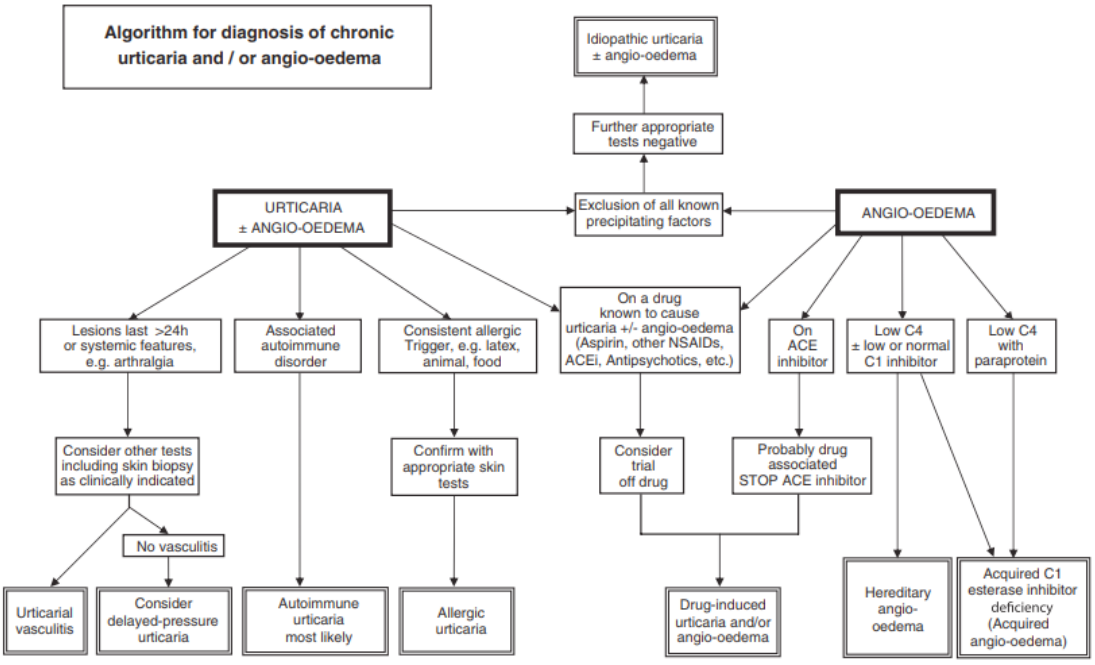

Fig. 1 Algorithm for differential diagnosis and approach to chronic urticaria:[112]

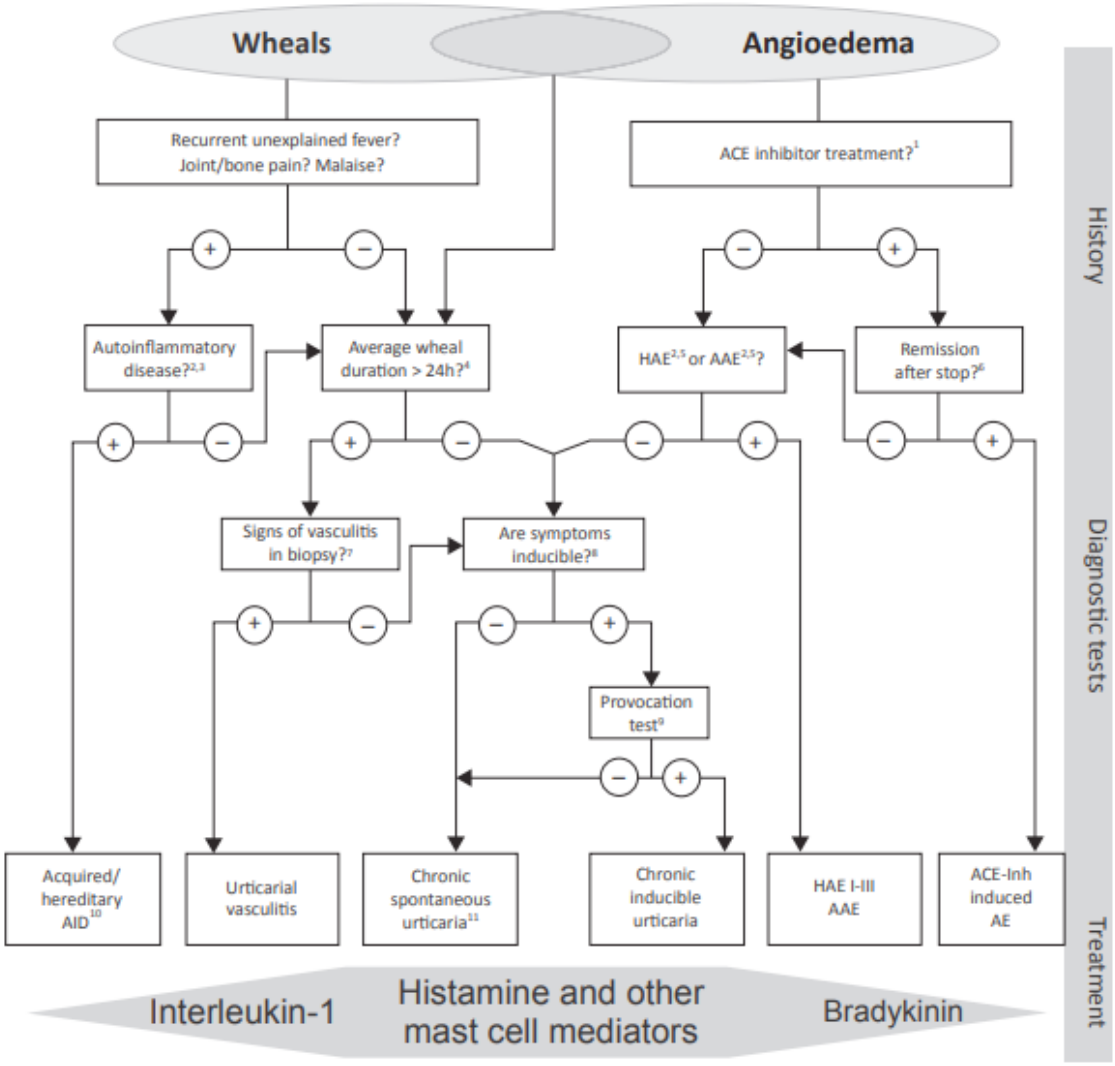

Fig. 2 Recommended diagnostic algorithm for chronic urticaria:[4]

TREATMENT

The treatment for each patient should be tailored to his/her symptom severity and aggravating factors. Any underlying infection should be treated, exacerbating drugs and food items should be avoided. Associated thyroid dysfunction and other relevant systemic diseases should be treated.

Pharmacotherapy:

First line agents: Newer generation H1 antihistamines should be preferred over the older generation H1 antihistamine. These include cetirizine, loratadine, desloratadine, fexofenadine and mizolastine. In pregnancy, chlorpheniramine and diphenhydramine are preferred oral and intravenous antihistamines respectively.[117] While hydroxyzine is preferred in cholinergic urticaria, cyproheptadine is preferred in cold induced urticaria.[118] If the patient doesn't respond to standard doses of non-sedating antihistamines, it is common to double or triple their doses.[119,120] It is now advised to updose an antihistamine instead of adding another antihistamine to maximize the benefits.[121] If response is still inadequate, then addition of tricyclic antidepressant like Doxepin, started at 10-25 mg in beginning to 75mg;[122] H2 antagonist;[123] mast cell stabilizer like ketotifen[124] can be considered.

Second line: Short course oral corticosteroids like prednisolone in the dose of 0.3-0.5 mg/kg, tapered over 4-6 weeks can be given in recalcitrant cases. While steroids shouldn't be given for long duration because of their side-effect profile, management of urticarial vasculitis requires use of oral corticosteroids.[116] Leukotriene receptor antagonist, Zafirleukast in dose of 20 mg twice daily and Monteleukast in dose of 10 mg once a day have shown superior efficacy in patients with urticaria aggravated by pseudoallergens.[125] Rofecoxib, a new COX2 inhibitor has also been given in patients of recalcitrant urticaria with success.[126]

Newer modalities in resistant cases:

While cyclosporine[127] has been tried with success in resistant cases, intravenous immunoglobulin has also shown benefit.[128]

Omalizumab 150-300 mg once or twice a month has shown improvement in reducing frequency and severity of urticaria with improvement in quality of life.[129,130] Plasmapheresis,[126] sulphasalazine,[131] cyclophosphamide,[132] phototerapy[133] and nifedipine[134] have been tried with variable success.

While the first line management of autoimmune urticaria remains H1 antihistamines, resistant cases, especially ASST positive ones, have been successfully treated using cyclosporine 4-6 mg/kg/day.[135]

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