Chronic Urticaria : Expanding the Autoimmune Kaleidoscope

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Introduction

Urticaria (from Latin *urtica* disica = stinging nettle) was described in 1772 by Herberden[1] as “little elevations upon the skin in the ‘nettle’ rash that often appears involuntarily and seldom stay many hours in the same place. There is nobody exempt from ‘them’ and by far the greatest number experience no other evil from it besides the intolerable anguish arising from the itching...” a clinical definition that has hardly been improved upon to date.

Urticaria is a vascular reaction pattern affecting 1/5th of the population sometime or the other in their lives, whose primary lesions of wheal appear suddenly as red, raised, itchy circumscribed areas of dermal oedema, last for a few hours and then fade away to reappear in the same or other places.

However, in around 30% patients of urticaria, attacks often recur for months or years, being labelled as chronic urticaria (CU) if attacks occur atleast twice a week for six weeks[2]. The same reaction in the deeper dermis and subcutaneous tissue, called angioedema, occurs concurrently in almost 50% of CU patients.

Affecting middle aged women more than men, CU is an indolent disease, testing the patience of both the patient and the doctor. Assessment of the impact of CU on the quality of life showed that these patients suffer similar disability, handicap and reduction of quality of life and higher sleep disturbance scores than patients with IHD [3].

Though CU is a tissue reaction pattern of diverse aetiologies (Fig 1), many cases previously regarded as idiopathic and labelled chronic idiopathic urticaria (CIU), are now being ascribed to autoimmunity. Still in many, the cause remains obscure.

Pathogenesis

Urticaria can occur by three of the four immunologic reactions as classified by Gell and Coombs. Type I, or the immediate IgE-mediated mechanism (“allergic” hive or acute urticaria), type II or the cytotoxic mechanism (urticarial phase of bullous pemphigoid) and type III or immune complex disease, as seen in serum sickness, SLE and rheumatoid arthritis, in which lesions are less pruritic, more persistent, often painful and may be associated with arthritis and other systemic features of vasculitis.

Noxious stimuli, on encountering the keratinocytes, induce the release of a melange of cytokines like interleukin 1(IL 1), IL3, IL6 IL8, granulocyte macrophage colony-stimulating factor and tumour necrosis factor alpha. These cytokines then signal to the migratory dendritic professional antigen presenting epidermal Langerhan’s cells or (dermal) mast cells, the appropriate inflammatory response to rally against that stimulus. The mast cells, which patrol the vasculature and nerve endings, on this signal, release their many (combinations of) performed and newly synthesized mediators (Fig 2).

Antigen-induced mast cell degranulation is a unique feature of type I (Gell and Coombs) reactions (acute urticaria). These type I reactions are often biphasic, with an early immediate phase (resulting from the release of the mast cell’s preformed mediators) occurring within 30 minutes, and a late phase (owing partly to the release of newly formed mediators and partly to the release of mediators from the other infiltrating inflammatory cells) that may occur 6 to 8 hours later.

It has been noticed that patients with CIU exhibit no recognizable late-phase reaction, suggesting that “allergy” (IgE) is probably not the dominant pathogenic

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Fig. 1 : Chronic urticaria - diverse aetiology

mechanism.

Chronic urticaria lesions demonstrate an infiltration of basophils, eosinophils and monocytes. A “concoction” of chemical mediators determined by the specific secretagogue or trigger, is then released by this cellular infiltrate.

Mast cells and basophils, the predominant sources of the body’s histamine have much in common in their mediator content and mechanism of release. Mast cells themselves, in different locations however have differences in mediator content, sensitivity to secretagogues and response to pharmacologic agents.

The mechanism of degranulation has been best studied with IgE as a secretagogue. IgE antibody binds with its specific, high-affinity receptor on the surface of the mast cell. Binding is rapid, tight, persistent and sensitive. When a threshold number of receptors are “bridged” (1% or fewer of a cell’s receptors), the mast cell membrane becomes activated (via the arachidonic acid metabolic pathway), and there is a rapid influx of Ca^{++} ions from the intercellular space into the mast cell. Neither basophils nor non-IgE secretagogues require calcium for activation. A concomitant generation of intracellular cAMP and the presence of Ca^{++} initiate movement of the granules toward the cell surface where they fuse with the cell membrane, and secrete their contents into the extracellular space [4].

It is not clear whether the numbers of cutaneous mast cells in chronic urticaria are increased or unchanged, but they definitely respond with a lowered threshold of releasability [5]. Secretagogues trigger mast cell and basophil mediator release immunologically through identifiable receptors on the mast cell surface (Fig 3)

Fig. 2 : Mast cell degranulation

and nonimmunologically without receptor mediation. Therefore CU can be classified as immunologic (mediated by IgE or IgE receptors), complement mediated due to direct mast cell degranulation and related to abnormal arachidonic acid metabolism (Table 1).

Autoimmune urticaria

The concept of autoimmune urticaria has evolved over the past decade as evidence for histamine-releasing autoantibodies and their relationship to disease activity has accrued. Several lines of evidence support this concept. The frequency of atopy in these patients is equal to the general population and serum IgE levels are usually normal. Biopsies of lesions of CU reveal a perivascular accumulation of eosinophils, mast cells and activated CD4^{+} T cells, in contrast to biopsies of lesions in acute urticaria, which are devoid of cellular infiltrates.

Recently IgG class autoantibodies against IgE and/or the high-affinity IgE receptor on mast cells (FcεRI) (Fig 3) have been demonstrated in the serum of patients with CU [6]. Many autoimmune diseases have also been reported as associated with CU including thyroid disease, celiac disease, insulin-dependent diabetes mellitus (IDDM), ulcerative colitis and others [7].

Spontaneous urticarial lesions were observed in 7 out of 12 CIU patients after an autologous serum injection in 1982 [8]. The response was not seen in healthy subjects. It was also found that the presence of this serum factor related to overall disease activity and might therefore be relevant to its pathogenesis. This autologous serum test (ASST) could be transferred passively to healthy volunteers. Pre-treatment with

Table 1**Secretagogues: pathogenetic classification of urticaria**

- I. Immunologic activation (receptors on cell membrane)
 - a. IgE dependent type I Gell and Coombs-type reaction - more important in acute urticaria
 - b. IgG antibodies against IgE receptor (FcεRIa)-more important in CU
 - c. Neuropeptides: substance P, somatostatin, gastrin
 - d. Immune complexes: type III Gell and Coombs reaction
 - (1) Direct by bridging receptors, eg: serum sickness, vasculitis, infection (viral)
 - (2) Via complement activation, C3a, C5a, eg: hereditary or acquired angioedema
- II. Nonimmunologic activation
 - a. Direct effect on mast cells
Radiocontrast media, opiates (morphine, codeine), antibiotics (especially...lactams), peptides found in jellyfish, lobsters, and strawberries, irradiation, curare, dextran and physical: heat, pressure, ultraviolet light, vibration, water
 - b. Complement activation
Radiocontrast media, blood products
 - c. Modulation of mast cell responsiveness
 - (1) Via the arachidonic acid metabolic pathway, eg: NSAIDs, dietary salicylates, "berries," benzoates, preservatives, dyes
 - (2) Cytokines, HRF (histamine releasing factor), IL1
- III. Mechanism unknown
Alcohol, amphetamine, rifampicin, thiamine, thiopental

antihistamines or the mast cell-degranulating chemical compound 48/80 substantially reduced the response, suggesting that it was histamine and mast cell dependent [9].

Detailed study of these sera and IgG purified from them showed that they contained functional autoantibodies directed against the α -subunit of the high-affinity IgE receptor (FcεRI α) on basophils and mast cells [10]. These anti-FcεRI α autoantibodies can be either competitive or noncompetitive [11]. Autoimmune conditions (thyroid disease, vitiligo, insulin-dependent diabetes, rheumatoid arthritis and pernicious anemia) are associated more frequently with chronic urticaria patients having functional autoantibodies than in those without autoantibodies [12].

A strong association has recently been shown between in vitro basophil histamine-releasing activity and HLA-DR4 and its associated allele DQ8 in chronic urticaria patients with a positive ASST response [13].

Autoantibody assays: Skin mast cells have been used as target cells in a few studies, but are more difficult to obtain and require a different source for each experiment. Most immunoassays therefore use donor basophils. Ferrer, Kinet, and Kaplan [6] have found anti-FcεRI α autoantibodies by Western blotting in a high proportion of chronic urticaria sera. Fiebiger et al [14] have developed an enzyme-linked immunosorbent assay

Fig. 3 : Mast cell secretagogues (immunological)

(ELISA) for anti-FcεRI α autoantibodies, which allows large numbers of sera to be screened.

The basophil histamine release assay, currently the "gold standard" for detecting functional autoantibodies in serum of patients with chronic urticaria, is difficult to standardize because it requires fresh basophils from healthy donors and is time consuming. Western blotting and other nonfunctional assays, including enzyme-linked immunosorbent assay (ELISA) and flow cytometry using chimeric cell lines expressing the human FcεRI α , may be useful for screening sera in the future but need to be validated. The finding that peripheral blood basophils are reduced or absent in patients with chronic urticaria with histamine-releasing autoantibodies [15] may prove to be a helpful clinical marker of autoimmune urticaria once rapid and reliable methods for measuring small numbers of circulating basophils are available.

Physical urticaria

The wheals in physical urticaria, the commonest form of chronic urticaria, occur in response to an inciting physical stimulus, in limited areas and are more prevalent among younger adults. In some patients, more than one type may be present.

Dermographism: An exaggerated triple response of Lewis seen on stroking the skin firmly, especially on areas that are not subject to pressure or friction and are sun protected, is associated with various pathologic and physiologic conditions such as urticaria pigmentosa (Darier's sign), hypothyroidism or hyperthyroidism, diabetes mellitus, infectious diseases (especially viral), scabies, hymenoptera stings, phenylketonurea, drugs especially penicillin, on tattoo sites, pregnancy and menopause. When accompanied by pruritus, it is called symptomatic dermographism.

Treatment

Though H₁ antihistamines like hydroxyzine, cetirizine and cyproheptadine alone or better still in combination with H₂ receptor blockers form the mainstay of treatment, regular exposure to ultraviolet light therapy can be helpful. Loosely fitting clothing is advocated.

Cold urticaria: The development of wheals after exposure to cold can be familial, acquired or secondary. 96% of cases of cold urticaria are secondary and develop most often in young adults frequently following stress, viral illness or multiple insect bites. Wheals develop within minutes upon rewarming of the involved sites. Mucous membranes or the tongue may be affected. A change in skin temperature, not absolute skin temperature, is important for the generation of the lesions. Bronchospasm, angioedema, hypotension, flushing and even death due to drowning on cold water exposure have been reported.

Diagnosis

Acquired cold urticarias are diagnosed by cold contact stimulation tests, with application of an ice cube to the skin for 10-20 minutes.

Treatment

The cardinal objective is the prevention of shock reactions during aquatic and other cold exposures. Antihistamines administered 30 to 60 minutes before cold exposure are effective in aborting urticarial episodes. Cyproheptadine HCl (2-4 mg three times a day) and doxepin (10-75 mg/day) are effective in the treatment of cold urticaria. Besides its H₁ antihistamine action, cyproheptadine has antiserotonin, anticholinergic and H₂ antihistamine activity. Desensitization has been shown to be beneficial.

Cholinergic urticaria: Small, 2 to 3 mm scattered wheals surrounded by large and erythematous flares are distinctive. Precipitating stimuli include exercise, warm temperature (increase in core temperature), ingestion of hot or spicy foods and emotional stress. The condition often remits within several years, but cases lasting for more than 20 years have been reported.

Diagnosis

Provocation by exercise or hot baths.

Treatment

Attacks of cholinergic urticaria can be aborted by the prompt application of cold water or ice to the skin after the induction of sweating. A refractory period of up to 24 hours can be induced by a carefully taken hot bath or exercise. Cholinergic urticaria responds better to hydroxyzine.

Solar urticaria: A rare disorder in which erythema is followed by a pruritic wheal within 5 minutes of exposure to an appropriate wavelength of light. Lesions usually fade within 15 minutes to 3 hours. Chronically sun exposed skin often displays a reduced reaction.

Diagnosis

A phototesting reaction noted within 5 to 10 minutes of exposure to a monochromator or a hot quartz lamp, or sunlight is diagnostic [16].

Treatment

Topical sunscreens are frequently disappointing. Chloroquine (500 mg/day), beta-carotene and PUVA have been used successfully in a few cases.

Pressure urticaria: Usually chronic, occurs after 4 to 6 hours of pressure to the skin as erythematous, "deep", nonpruritic and usually painful hives.

Diagnosis

A pressure challenge of 15 pounds on the shoulder for 15 minutes is applied as a provocation test [16].

Treatment

Antihistamines are disappointing, but most pressure lesions improve with NSAIDs. Systemic steroids (prednisilone, 40 mg/day) may be indicated in some patients who have both chronic urticaria and pressure urticaria.

Aquagenic urticaria: Develops in areas in contact with water. The pruritic, follicular and cholinergic-like wheals appear within 2 to 3 minutes to half an hour of immersion.

Diagnosis

Application of water compresses (35-36° C) to the patient's back for up to 30 minutes [16]. Some recommend patch testing to scalp sebum and sweat (for 10 minutes) [16].

Treatment

Therapy with antihistamines is only partially effective. Coating the skin with inert oil may be protective.

Vibratory urticaria: Develops within 5 minutes of massage or other vibratory movements.

Diagnosis and Treatment

The provocative test involves application of a kitchen mixer to the patient's forearm. There is no known effective treatment, except avoiding inciting stimuli.

Urticarial vasculitis

Normocomplementaemic urticarial vasculitis is usually idiopathic, but hypocomplementaemic urticarial vasculitis may be associated with underlying SLE, Sjogren's syndrome or cryoglobulinemia (which itself is closely linked with hepatitis B or C virus infection). Primary urticarial vasculitis can occasionally evolve into SLE [17].

Diagnosis

A differential diagnosis of urticarial vasculitis is one of the few indications for carrying out a skin biopsy in CU.

Skin biopsy: Histological criteria for diagnosis of urticarial vasculitis include a predominantly neutrophilic perivascular infiltrate, nuclear dust, extravasated erythrocytes and fibrinoid necrosis of vessel walls.

Treatment

H₁ antihistamines and corticosteroids (upto 2mg/kg/day) may be tried but are often ineffective. Other drugs given for unresponsive cases are colchicine 0.5-1.5 mg/day, dapsone 50-100 mg/day, hydroxychloroquine 400 mg/day, cyclophosphamide 1.5 mg/kg/day and methotrexate 12.5-25 mg/week as pulse therapy.

Infection related

Viruses like HBV, HCV, HSV etc; bacteria like *Streptococci*, *M tuberculosis*, *T pallidum* and protozoa like *entaamoeba*, *giardia* etc; have all been implicated and eradication of infective foci may be helpful. A possible role for *Helicobacter pylori* gastritis in etiology of CU by evoking autoantibody production due to molecular mimicry has also been proposed [18].

Pseudoallergic reactions

These are anaphylactoid reactions (non-IgE mediated) caused by food additives, flavouring agents, preservatives, fruits like strawberry and natural dietary salicylates.

Diagnosis of a case of chronic urticaria

The timing of onset and duration of individual wheals may be very helpful in giving a clue to the aetiology (Fig 4). Morphology of the wheals can be informative in physical urticarias, such as linear lesions of dermatographism or small papular wheals of cholinergic urticaria. Distribution may suggest a cause, such as predilection for palms, soles and lower back in delayed pressure urticaria or the restriction to light-exposed skin in solar urticaria. General and systemic examination for

Fig. 4: Duration of wheals is pointer to aetiology in chronic urticaria

associated systemic and autoimmune disease should never be overlooked. Skin biopsy is helpful in diagnosing urticarial vasculitis.

Recent diagnostic guidelines recommend thorough and repeated history taking as the best investigation supplemented with limited laboratory investigations [19] like CBC, ESR, urinalysis and stool for ova and cysts. Further tests like blood chemistry, liver and renal function tests, ANA, HBV and HCV antigen or antibodies, anti-thyroid antibodies, plasma and erythrocyte protoporphyrins and CH 50 (hereditary C1 esterase deficiency) may be carried out only if indicated by history.

Newer modalities are becoming available for diagnosing autoimmune urticaria like IgE and IgE receptor antibody assay, basophil histamine release assay, Western blotting and ELISA though further validation studies are required. ASST remains the in vivo investigation of choice in CU (sensitivity-70%, specificity-80%).

Treatment of chronic urticaria

Of the many pharmacologic and non-pharmacologic interventions, none is universally successful and so treatment has to be tailored individually and includes avoidance of trigger factor, if any found, by lifestyle modification. This is especially useful in physical urticarias and urticaria due to NSAIDs and dietary pseudoallergens. Advice to the patient must be detailed and specific. He may need suitable support and education in view of the significant potential of physical,

psychological, social and economic handicaps due to the disease.

First-line drug therapies

Oral antihistamines, the mainstay of drug treatment for chronic urticaria reduce itch, whealing or both. Newer non-sedating antihistamines are widely available now (Table 2). It is becoming common practice in the West to exceed the licensed dose due to additional benefits from stabilizing mast cells, inhibitory effects on adhesion molecule expression and eosinophil chemotaxis [20]. However their use in pregnancy and childhood should be cautious, the safest one in pregnancy being chlorpheniramine. Addition at night of a sedating antihistamine, such as chlorpheniramine, hydroxyzine, or diphenhydramine, is helpful when sleep is disturbed by itching. Combining H₁ and H₂ receptor antagonists though sound theoretically has been unimpressive clinically.

Table 2
Newer non-sedating antihistamines

Generic name	Daily dose (mg)
Cetirizine	10
Fexofenadine	180
Loratadine (anti-inflammatory)	10
Desloratadine	5
Mizolastine	5

Oral corticosteroids

Severe exacerbations of chronic urticaria that have not responded to full-dose antihistamines, delayed pressure urticaria and urticarial vasculitis (which respond poorly, if at all) may require oral corticosteroids in short reducing doses. Long-term administration of corticosteroids should be avoided by introducing steroid-sparing therapies, where possible. Low-dose alternate-day corticosteroids may be appropriate when long term use is inescapable[21].

Other interventions for antihistamine unresponsive CU

Thyroxine has been used in euthyroid patients with positive thyroid autoantibodies. *H. pylori* eradication therapies in chronic urticaria, [22] nifedipine for chronic urticaria, [23] sulfasalazine in delayed pressure urticaria, [24] and leukotriene receptor antagonists in aspirin-sensitive urticaria [25] have been successful. Drugs like colchicine, hydroxychloroquine, dapsone and indomethacin have been used successfully in urticarial vasculitis.

Third-line drug therapies (immunosuppressive)

Immunosuppressive therapy is becoming a realistic option in some patients in whom chronic urticaria proves

to have an autoimmune basis, but only when it is pursuing a severe disabling course. Plasmapheresis, [26] intravenous immunoglobulins (2 g over 5 days) [27], cyclosporine (2.5-5 mg/kg per day) [28] have all been successful. Other immunosuppressive therapies, such as azathioprine, methotrexate or mycophenolate mofetil, may also be useful but protocols need to be developed to define optimal treatment regimens.

Future treatment modalities

Therapeutic antibodies, such as humanized monoclonal anti-IgE, anti-TNF- α , anti-IL5 and DNA plasmid vaccination to induce tolerance to the α -chain are the hope of the future.

Conclusion

Considerable disability and even death can result from CU/angioedema, reaction patterns of diverse etiologies. Though clinical and historical cues along with relevant investigations help unravel the possible cause in a vast majority, some cases defy all efforts. Recent research into the kaleidoscope of chronic urticaria has revealed many recalcitrant cases of so-called CIU to have definite autoimmune basis and accelerated the addition of biological options like peptides and antibodies (IgE receptor specific, anti IgE, Anti TNF α and anti-IL5) to traditional treatment modalities (immunosuppressives, plasmapheresis, leukotriene antagonists, IVIg, etc.) of autoimmune disorders.

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