Urticaria occurs commonly in children and young adults. In general, a younger and atopic population is usually involved and the lesions are acute, usually less than 6 weeks in duration and it is relatively easy to show a cause and effect, usually by history. The cause of chronic urticaria, which is defined as urticaria lasting longer than 6 weeks, is much more difficult to identify and 80–95% of patients are classified as idiopathic. Many of the patients react with a wheal and flare to their own serum or plasma indicating that they have a histamine-releasing agent in their own serum. Most of these subjects will have urticaria which clears with time but a small minority continue to have urticaria for the rest of their lives.

Treatment for patients having known causes is to avoid the triggers and all patients with chronic urticaria need to be treated with H1 antihistamines. Sometimes an H2 antihistamine is added or a tricyclic ‘tranquilizer’ which has anti H1 and H2 blocking action needs to be used. Those patients who do not respond may need treatment with prednisone which should be reduced to the smallest dosage and discontinued as soon as possible. Patients with hereditary angioedema respond to danazol, stanozol or epsilonaminocaproic acid or tranexamic acid.

Key words: angioedema, hives, incidence, treatment

Pathogenesis
The mast cell is critical to the pathogenesis process. The characteristic wheal and flare was produced in normal skin by Sir Thomas Lewis in 1927 by the intracutaneous injection of histamine. Mast cells can be induced to release histamine and other inflammatory mediators by a variety of processes. These include non-immunologic, immunologic and genetic factors.

Non-immunologic factors include: (i) chemical histamine liberators such as opiates, curare and polymyxin B; (ii) direct effects of physical agents; (iii) cholinergic effects via heat or increased blood supply to the skin and defects of the non-adrenergic non-cholinergic system. Immunologic factors complement activation by the classic or alternative pathways, anaphylatoxins (C3a and C5a) and IgE mediated allergy. Genetic factors include a deficiency in various complement factors and modulating factors, including hormones, autoantibodies and aggravating influences.

Figure 2 is a diagrammatic representation of the interactions that cause a wheal and flare, including the release of histamine and of substance P. Antigen or IgE antibody cross-links several receptors on the surface of the mast cell. This cell then releases a variety of factors including pre-formed and newly formed factors. In addition, afferent cutaneous nerves will release such neurogenic factors as substance P which has a direct effect on the blood vessels. These are active factors which are potential mediators of urticaria and angioedema. The sources of these...
active agents are cutaneous mast cells which release histamine, prostaglandin D2, leukotrienes C and D, platelet-activating factor and the kallikrein-like enzyme, bradykinin. The complement system releases anaphylatoxins C3a, C4a, C5a and histamine. The Hageman factor-dependent pathway release bradykinin and mononuclear cells release a variety of histamine-releasing factors.3

Increased vascular permeability leads to activation of the plasma kinin system and Hageman factor activation with formation of bradykinin. The interplay of mononuclear cell T and B lymphocytes and monocytes release histamine and other vasoactive factors from basophils and mast cells.4 Histamine causes vascular permeability, edema, vasodilation and erythema (increased blood supply) causing a flare in the skin. Histologically one sees the dilation of small vessels, widened dermal papillae, flattened reti pegs, separation of collagen bundles and lesions occurring in the superficial dermis.5

Figure 3 shows the epidemiology of hives. The incidence rate increases from 3.5 per 100,000 individuals at age 5 years to 12 per 100,000 by 20-40 years of age. Hives incidence then decreases steadily to 2 per 100,000 by age 70 years.6

Figure 4 shows the average duration of urticaria. Half of those with urticaria will clear in 1 year and three-quarters will clear in 5 years. By 10 years one-fifth of the subjects with chronic urticaria will still have problems which may be ongoing.7

The overall known causes of acute and chronic urticaria are drugs, foods, food additives, inhalant, ingestant or contact allergens, a variety of parasitic, bacterial and fungal infections, insect stings, urticaria pigmentosa or systemic mastocytosis, autoimmune diseases, malignancies, endocrine diseases, hereditary diseases, transfusion reactions, physical urticaria, and autoimmune conditions. However, the cause of chronic urticaria is unknown in 80-95% of patients.
Drugs

Penicillins are the most common and best studied cause of urticaria from drugs.\(^8\) Chemotherapeutic sulfonamides and other agents of that group, including sulfonurea oral hypoglycemia agents, thiazide diuretics, furosemide, carbonic anhydrase inhibitors and procaine-type local anesthetics have been known to cause urticaria. Aspirin and other non-steroidal anti-inflammatory drugs (NSAID), radioccontrast dyes and other substances can also induce urticaria.\(^9\)

Foods and food additives

Among the foods responsible for causing reactions (IgE mediated) are shell fish, fish, eggs, peanuts, nuts and fruits in adults, and eggs, milk and peanuts in children.\(^10\) Food additives are probably not IgE mediated and they include tartrazine, sulfites, benzoates and, perhaps, natural salicylates.\(^11\) And finally, inhalant and contactant allergens may be IgE mediated. All the usual inhalant allergens are capable of inducing urticaria via IgE pathways.

Infections

In the infectious category are viral infections such as infectious hepatitis, infectious mononucleosis and a variety of others. In some patients there is a possible relationship to group A Beta streptococcal infections and urticaria. Fungal infections and parasitic infections such as ascari, ancylostoma, strongyloides, filaria, echinococcus, schistosoma, trichinella, toxocara and fasciola also have been implicated but rarely cause urticaria even in endemic areas.

Insects

Insect bites and stings can cause urticaria. The most prominent among them are hymenoptera stings from wasps, yellow jackets, hornets, bees and fire ants. Papular urticaria results from flea bites, swimmer’s itch and possibly mosquito bites, and may be confused with hives. However, if one outlines a lesion with ink, the lesion will be present for several days which is not characteristic of urticaria which remains for only a few hours and then moves on to other sites.

Other causes

Urticaria pigmentosa and systemic mastocytosis will result in pigmented nevi over the bodies of children. When they are rubbed they urticate because histamine is released from skin
mast cells. Autoimmune diseases including systemic lupus erythematosus, serum sickness, cutaneous vasculitis, Sjogren’s Syndrome and rheumatoid arthritis are autoimmune diseases, which may have urticaria as symptoms. Fortunately they are all associated with an elevated sedimentation rate which is a definite factor in diagnosis. Malignancies rarely induce urticaria. Those that do are lymphoma and Hodgkin’s disease. Endocrine diseases both hyper and hypothyroidism and hyperparathyroidism can result in urticaria. Estrogen in some patients can cause urticaria.\textsuperscript{12,13}

Hereditary disease

Hereditary urticaria includes hereditary C1 inhibitor deficiency angioedema.\textsuperscript{14} Clinically, one has recurrent attacks of angioedema with laryngeal and gastrointestinal involvement which do not respond to epinephrine. On laboratory examination the C1 inhibitor is low in 85% of cases and may be normal or elevated but non-functional in 15% of cases. The C4 is lower during attacks and but less depressed between attacks. C1 deficiency levels in acquired angioedema are low but are normal in the hereditary disease; C1q binding is elevated in the acquired but normal in the hereditary disease. The hereditary type is an autosomal dominant disease. The acquired type that occurs with malignancy, lymphoma and carcinoma also occurs with auto-antibodies to the C1 inhibitor which render it non-functional.

Hereditary vibratory angioedema is a very rare autosomal recessive disease. Familial urticaria with amyloidosis and deafness is very rare and is a dominant disease.

Physical urticarias

Physical urticaria includes idiopathic cold urticaria with a development of hives at local sites of cold contact. Occasionally it is IgE mediated and can be transferred by serum to another subject by injecting it intradermally. It is confirmed by placing an ice cube on the skin of the patient for 5 min. There is also a cold urticaria associated with cold agglutinins, cryoglobulins and cryofibrinogen.\textsuperscript{15} Cholinergic urticaria is associated with small, punctate wheals with large flares induced by exercise, sweating, anxiety or hot showers. It may be associated with a fall in lung function. Exercise-induced anaphylaxis is precipitated by exercise and sometimes associated with foods such as celery but it is often associated with eating. It occurs 5–30 min after exercise and it may last between 1 and 3 h. It may be associated with a spectrum of anaphylactic symptoms and pulmonary function does not fall, and it is not associated with the heating of the body.

Symptomatic dermatographism is present in a small number of the 2–5% of the general population that has dermatographism. It is precipitated by gentle stroking of the skin which results in a large wheal and flare within approximately 5 min. In some people there has been a transferable factor identified. Other forms of physical urticaria include delayed pressure urticaria, heat urticaria, aquagenic urticaria, solar urticaria and vibratory angioedema.

Chronic idiopathic urticaria occurs in 80–95% of individuals with chronic urticaria. The patients do not have atopic diseases as IgE levels are frequently normal but not always. Urticaria can be mild or severe. On biopsy, one sees a non-necrotizing perivascular infiltrate, a ten-fold increase in the number of mast cells and a four-fold increase in the number of mononuclear cells. Activated CD4 helper T cells are also increased and there may be increased depositions of eosinophil basic protein in skin lesions.\textsuperscript{16}

Evaluation

In the evaluation of patients with chronic urticaria a history is important. One should inquire about the time of onset and whether it occurred abruptly or insidiously, the frequency of the eruption, possible triggers and the family prevalence of urticaria. On physical examination one should look at the skin lesions, possibly outlining them in ink, and should examine for signs of atopy such as nasal congestion or wheezing. A painful anterior neck suggests thyroiditis; nodes enlarged over the body suggest such factors as infectious mononucleosis, lymphoma or Hodgkin’s disease. Beta-hemolytic symptoms are evidenced by a red throat with enlarged glands in the neck only. One should also examine for arthritis, edema which suggests kidney disease, and examine the eyes for the dryness of Sjogren’s syndrome.

The laboratory tests are selected on the basis of the history and physical examination. In atopic patients, prick tests may be required for foods, or prick and intradermal tests for inhalant factors. A complete blood count and differential and sedimentation rate should be determined in patients with chronic urticaria. While with the patient, gentle stroking of the skin will reveal dermatographism 5–15 min later. Direct exposure to an ice cube for 5 min will reveal cold-induced urticaria. If one suspects cholinergic urticaria the injection of 100 μg of methacholine directly into the skin will produce a wheal and flare. The differential between heat-induced and exercise-induced anaphylaxis can be identified by doing an exercise test for 10 min at 80% of cardiac output in a plastic rain suit. A fall in lung function with small punctate hives suggests cholinergic urticaria while signs of anaphylaxis without change in lung function suggests exercise-induced anaphylaxis.

Treatment

The treatment of urticaria involves avoidance of physical stimuli, drugs, if they are the cause, food and additives which induce hives, and also avoidance of modulating factors such as emotions, exertion and alcohol. Prescribing antihistamines with cyproheptadine is recommended in the US for cold urticaria, but ketotifen (not available in the US but available in Japan)
seems to be a very effective agent for its prevention. Other anti-
histamines include astemizole,17 terfenadine and hydroxyzine.18
Antihistamine drugs should be taken regularly and not on an "as
needed" basis. Cholinergic urticaria or symptomatic dermato-
graphism is treated with hydroxyzine or cetirizine. Cetirizine is
not as sedating as hydroxyzine and is formed when hydroxyzine
is metabolized in the liver. The second generation antihista-
mines have been used for other forms of urticaria. Epinephrine
may be administered subcutaneously for acute swelling of
the throat or mouth, but will have no effect on hereditary
angioedema.

Cimetidine or ranitidine (H2 blockers) have been used com-
bined with H1 antihistamine when H1 blockers by themselves
are ineffective. Tricyclic compounds such as doxepin which have
an H1 and H2 blocking action have also been prescribed. In
the cases where the antihistamines fail to work, oral cortico-
steroids are prescribed. Once improvement occurs the dosage
may be tapered to the smallest effective amount and then
administered every other day. The dose is then gradually
reduced until the steroid can be discontinued. In hereditary or
acquired angioedema, anabolic synthetic steroids such as
danazol or stanozolol have been used and seem to be effective
in preventing further attacks in some patients, as is epsilon-
aminocaproic acid and tranexamic acid. Swelling of the larynx
may necessitate a tracheotomy.

In summary, most of the cases of urticaria occur without a
known cause and a major goal of therapy is symptom relief. The
primary drugs are H1 and, possibly, the H2 antihistamines. The
antihistamines must be used regularly and not as needed.
Steroids should be added if the subject breaks through antihist-
amine therapy. Reduce the steroids to the smallest possible dose
and then give every other day, finally discontinuing the steroids
as soon as possible.

**DISCUSSION**

Hide et al. described 20 patients in a group of 25 who reacted
to their own serum or plasma with a wheal and flare when it was
injected intradermally.19 They read the histamine reaction at half
an hour and the intradermal serum reaction at 1 hour. These
patients had low IgE levels in their blood. Further in vitro tests
showed that the reaction could be blocked by adding IgE to the
serum or removing IgE. They also noted that these patients with
a positive skin test to their own serum had lower levels of IgE
than those who did not. Accordingly, they hypothesized that it
may be due to an IgG in the patients’ serum which was directed
against the high affinity IgE receptor.

We did a similar study where the study group consisted of 8
males and 17 females with chronic urticaria.20 There was one
child under 12 years of age, four patients who were adolescent
between 13 and 18 years and 20 adults. The adults ranged in
age from 19 to 63 years. Eleven patients had either hay fever
or asthma as well as chronic urticaria, three had symptomatic
dermatographism and 11 patients had idiopathic urticaria. IgE
levels were done on these patients. The mean level of the atopic
patients was 171.25 ± 80.45 IU (± SD) not including the one
patient who had an IgE level of 1490 IU. The level in the der-
matographism patients was 13 IU. Those with idiopathic urti-
caria had an average level of 55.0 ± 46 IU (± SD). Each of
these patients had skin tested with 5 µL of autologous serum or
plasma which was read at 15 min and 1 h, and with histo-
mine in the concentration of 27.5 µg/mL which was read in half
hour intervals. A wheal measuring 5 mm or greater than the
saline control was considered a positive reaction. There was a
statistically significant difference in IgE levels between those who
were atopic and those with only idiopathic urticaria. All patients
reacted to control histamine injection proving that they had not
taken anything that would interfere with a positive skin test when
tested with 0.02 mL of autologous serum. The results are shown
in Table 1.

Patients who have a positive skin test to their own serum or
plasma have a histamine releasing factor in their serum. It is
not yet known what this factor is. However, we can predict that these
patients will be harder to treat than those with negative tests.
Few of the patients in our study had the low IgE levels noted by
Hide et al. Indeed most of those with negative skin tests
responded to H1 antihistamines, while some of those with posi-
tive skin tests frequently required a drug with H2 blocking action
or a systemic corticosteroid in their early therapy.

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