resolution of cold urticaria by treatment with monoclonal anti-human IgE (omalizumab). Elevations of plasma histamine levels with biopsy-proven mast cell degranulation have also been demonstrated with generalized attacks of *cholinergic urticaria* and *exercise-related anaphylaxis* precipitated experimentally in subjects exercising on a treadmill while wearing a wet suit; however, only subjects with cholinergic urticaria have a concomitant decrease in pulmonary function.

Up to 40% of patients with chronic urticaria have an autoimmune cause for their disease including autoantibodies to IgE (5–10%) or, more commonly, to the α chain of FcεRI (35–45%). In these patients, autologous serum injected into their own skin can induce a wheal-and-flare reaction involving mast cell activation. The presence of these antibodies can also be recognized by their capacity to release histamine or induce activation markers such as CD63 or CD203 on basophils. An association with antibodies to microsomal peroxidase and/or thyroglobulin has been observed often with clinically significant Hashimoto's thyroiditis. In vitro studies reveal that these autoantibodies can mediate basophil degranulation with enhancement by serum as a source of the anaphylatoxic fragment, C5a.

Hereditary angioedema is an autosomal dominant disease due to a deficiency of C1INH (type 1) in about 85% of patients and to a dysfunctional protein (type 2) in the remainder. A third type of hereditary angioedema has been described in which C1INH function is normal, and the causal lesion is a mutant form of factor XII, which leads to generation of excessive bradykinin. In the acquired form of C1INH deficiency, there is excessive consumption due either to immune complexes formed between anti-idiotypic antibody and monoclonal IgG presented by B cell lymphomas or to an autoantibody directed to C1INH. C1INH blocks the catalytic function of activated factor XII (Hageman factor) and of kallikrein, as well as the C1r/C1s components of C1. During clinical attacks of angioedema, C1INH-deficient patients have elevated plasma levels of bradykinin, particularly in the venous effluent of an involved extremity, and reduced levels of prekallikrein and high-molecular-weight kininogen, from which bradykinin is cleaved. The parallel decline in the complement substrates C4 and C2 reflects the action of activated C1 during such attacks. Mice with targeted disruption of the gene for C1INH exhibit a chronic increase in vascular permeability. The pathobiology is aggravated by administration of an ACE inhibitor (captopril) and is attenuated by breeding the C1INH null strain to a bradykinin 2 receptor (Bk2R) null strain. As ACE is also described as kininase II, the use of blockers results in impaired bradykinin degradation and explains the angioedema that occurs idiosyncratically in hypertensive patients with a normal C1INH. Bradykinin-mediated angioedema, whether caused by ACE inhibitors or by C1INH deficiency, is noteworthy for the conspicuous absence of concomitant urticaria.

DIAGNOSIS

The rapid onset and self-limited nature of urticarial and angioedematous eruptions are distinguishing features. Additional characteristics are the occurrence of the urticarial crops in various stages of evolution and the asymmetric distribution of the angioedema. Urticaria and/or angioedema involving IgE-dependent mechanisms are often appreciated by historic considerations implicating specific allergens or physical stimuli, by seasonal incidence, and by exposure to certain environments. Direct reproduction of the lesion with physical stimuli is particularly valuable because it so often establishes the cause of the lesion. The diagnosis of an environmental allergen based on the clinical history can be confirmed by skin testing or assay for allergen-specific IgE in serum. IgE-mediated urticaria and/or angioedema may or may not be associated with an elevation of total IgE or with peripheral eosinophilia. Fever, leukocytosis, and an elevated sedimentation rate are absent.

The classification of urticarial and angioedematous states presented in Table 376-1 in terms of possible mechanisms necessarily includes some differential diagnostic points. Hypocomplementemia is not observed in IgE-mediated mast cell disease and may reflect either an acquired abnormality generally attributed to the formation of immune complexes or a genetic or acquired deficiency of C1INH. Chronic recurrent urticaria, generally in females, associated with arthralgias, an elevated sedimentation rate, and normo- or hypocomplementemia suggests an underlying cutaneous necrotizing angiitis. Vasculitic urticaria typically persists longer than 72 h, whereas conventional urticaria often has a duration of 12–36 h. Confirmation depends on a biopsy that reveals cellular infiltration, nuclear debris, and fibrinoid necrosis of the venules. The same pathobiologic process accounts for the urticaria in association with such diseases as systemic lupus erythematosus or viral hepatitis with or without associated arteritis. Serum sickness per se or a similar clinical entity due to drugs includes not only urticaria but also pyrexia, lymphadenopathy, myalgia, and arthralgia or arthritis. Urticarial reactions to blood products or intravenous administration of immunoglobulin are defined by the event and generally are not progressive unless the recipient is IgA-deficient in the former case or the reagent is aggregated in the latter.

The diagnosis of hereditary angioedema is suggested not only by family history but also by the lack of pruritus and of urticarial lesions, the prominence of recurrent gastrointestinal attacks of colic, and episodes of laryngeal edema. Laboratory diagnosis depends on demonstrating a deficiency of C1INH antigen (type 1) or a nonfunctional protein (type 2) by a catalytic inhibition assay. While levels of C1 are normal, its substrates, C4 and C2, are chronically depleted and fall further during attacks due to the activation of additional C1. Patients with the acquired forms of C1INH deficiency have the same clinical manifestations but differ in the lack of a familial element. Furthermore, their sera exhibit a reduction of C1 function and C1q protein as well as C1INH, C4, and C2. Inborn C1INH deficiency and ACE inhibitor–elicited angioedema are associated with elevated levels of bradykinin. Lastly, type 3 hereditary angioedema is associated with normal levels of complement proteins.

Urticaria and angioedema are distinct from contact sensitivity, a vesicular eruption that progresses to chronic thickening of the skin with continued allergenic exposure. They also differ from atopic dermatitis, a condition that may present as erythema, edema, papules, vesiculation, and oozing proceeding to a subacute and chronic stage in which vesiculation is less marked or absent and scaling, fissuring, and lichenification predominate in a distribution that characteristically involves the flexor surfaces. In cutaneous mastocytosis, the reddish brown macules and papules, characteristic of urticaria pigmentosa, urticate with pruritus upon trauma; and in systemic mastocytosis, without or with urticaria pigmentosa, there is episodic systemic flushing with or without urtication but no angioedema.

TREATMENT URTICARIA AND ANGIOEDEMA

Identification and subsequent elimination of the etiologic factor(s) provide the most satisfactory therapeutic program; this approach is feasible to varying degrees with IgE-mediated reactions to allergens or physical stimuli. For most forms of urticaria, H_1 antihistamines such as chlorpheniramine or diphenhydramine effectively attenuate both urtication and pruritus, but because of their side effects, nonsedating agents such as loratadine, desloratadine, and fexofenadine, or low-sedating agents such as cetirizine or levocetirizine generally are used first. Cyproheptadine in dosages beginning at 8 mg and ranging up to 32 mg daily and especially hydroxyzine in dosages beginning at 40 mg and ranging up to 200 mg daily have proven effective when H_1 antihistamines fail. The addition of an H_2 antagonist such as cimetidine, ranitidine, or famotidine in conventional dosages may add benefit when H_1 antihistamines are inadequate. Doxepin, a dibenzoxepin tricyclic compound with both H_1 and H_2 receptor antagonist activity, is yet another alternative. A $CysLT_1$ receptor antagonist such as montelukast, 10 mg/d, or zafirlukast, 20 mg twice a day, can be important add-on therapy.

Topical glucocorticoids are of no value, and systemic glucocorticoids are generally avoided in idiopathic, allergen-induced, or physical urticarias due to their long-term toxicity. Systemic glucocorticoids are useful in the management of patients with pressure urticaria, vasculitic urticaria (especially with eosinophil prominence), idiopathic angioedema with or without urticaria, or chronic urticaria that responds poorly to conventional treatment. With persistent vasculitic urticaria, hydroxychloroquine, dapsone, or colchicine may be added to the regimen after hydroxyzine and before or