

Chronic Urticaria—New Concepts Regarding Pathogenesis and Treatment

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Introduction

Chronic urticaria has been considered a cutaneous disease of unknown origin which, when severe, causes significant morbidity. The disease occurs in virtually any age group, although it is most common between the ages of 20 and 40, predominantly in women. Hives can appear on virtually any part of the body, and may be present on most days of the week. Forty percent of patients also have angioedema. Angioedema of the lips is the most common manifestation, but angioedema involving the cheeks, periorbital region, tongue, pharynx, hands, and feet may be seen as well. It is equally common in atopic and nonatopic subjects, and in the typical case, no external allergen or environmental substance is identifiable as the cause.

Etiology

There have been many theories regarding the etiology of chronic urticaria and angioedema that have been considered during the past 50 years. Some of these include psychophysiologic disorders (*ie*, an anxiety manifestation), allergic reactions to food dyes, additives, or naturally occurring chemicals, infection with *Helicobacter pylori*, or, most recently, the notion that it is a cutaneous autoimmune disease. I believe this last consideration is supported by the most data and is likely to stand the test of time. The first clue that chronic urticaria might be autoimmune in origin is its association with Hashimoto's thyroiditis. The incidence of having antibodies to thyroglobulin or microsomal antigens or to both is close to 25%, and that is true even if thyroid function is normal. A small percentage of patients have Graves' disease, with antibody to the receptor for thyroid stimulating hormone. There is no increased incidence of systemic lupus erythematosus (SLE) or other connective tissue diseases in

patients with chronic urticaria in spite of the fact that patients with SLE may also have hives. A number of articles have appeared to indicate that a small percentage of patients with chronic urticaria, perhaps between 5% and 10%, have circulating anti-IgE antibodies that can cross-link IgE on the surface of basophils or mast cells, cause them to degranulate, and lead to hive formation. More importantly, however, were studies by Hide *et al.* in Malcolm Greaves' group [1], who first demonstrated that approximately one third of patients with chronic urticaria have a circulating IgG antibody directed to the α subunit of the IgE receptor. Thus, this antibody can cross-link IgE receptors directly and activate the target cells, in this instance the cutaneous mast cell. This autoantibody interacts predominantly with unoccupied receptors; thus, receptor occupancy by IgE itself is inhibitory. Although nonatopic persons may have a greater percentage of unoccupied receptors, atopic individuals with high IgE have increased receptor numbers that are proportional to the IgE level. We have shown that these antibodies are capable of activating the complement system and that the liberation of C5a also contributes to basophil and mast cell degranulation. Therefore, the activation of the cutaneous mast cells appears to be caused by a combination of direct cross-linking of the IgE receptor, or IgE itself, plus interaction of C5a with the mast cell C5a receptor. The relative importance of these may vary from patient to patient. Since C5a and mast cell products (including chemokines) are chemotactic for neutrophils, eosinophils, monocytes, and T lymphocytes, skin biopsy of chronic urticarial lesions reveals a perivascular infiltration of these cells. The infiltrate resembles that seen in allergic late-phase reactions, which is not surprising, since they are both dependent upon prior mast cell activation. But the presence of C5a may change the proportion of infiltrating cells. The T lymphocytes are almost exclusively CD4 (+) rather than CD8 (+) and they are either the Th0 subtype or a mixture of Th1 and Th2 cells, since both interferon gamma and interleukin 4 are produced. Again, this differs from classical allergic reactions that are heavily skewed toward the Th2 subtype of CD4 (+) T lymphocyte. It is important to emphasize, however, that these autoimmune considerations are not present in about 60% of patients, and this group remains "idiopathic". It is my bias that the majority of these are also autoimmune. However, the

underlying mechanisms are yet to be determined. Although those in whom autoantibodies are demonstrable appear to be somewhat more severely affected, the groups are extremely similar in clinical presentation, as well as tissue histology, and response to treatment.

Treatment

When chronic urticaria is severe, antihistamines are often insufficient to control symptoms. Our own approach for such severe patients once we have maximized antihistamine therapy (H1 + H2 receptor blockade) and added an antileukotriene agent is to employ alternate-day steroids with an average starting dose of 20 mg of prednisone every other day. The dose is slowly decreased incrementally with changes being made every 2 to 3 weeks. In this fashion, we greatly improve control of the disease (which, typically, slowly improves with time) and avoid the severe side effects of corticosteroid use that inevitably occur when it is given daily or even on alternate days in higher doses. I believe the number-one error in treating severe chronic urticaria and angioedema based on those in patients referred to me is the employment of excessive doses of

corticosteroid with the doses of other modalities being too low. But the second most common error is not using corticosteroids at all when all else has failed. Experimental approaches to this disease have included trials of methotrexate, cyclosporine, intravenous gammaglobulin, plasmapheresis, Plaquenil (hydroxychloroquine, Sanofi-Synthelabo, New York, NY), sulfasalazine, and colchicine. Of these, the only one that I have found to be effective is cyclosporine, which we employ in patients refractory even to the aforementioned approach with corticosteroid. Plasmapheresis, although also effective, is impractical, but its efficacy provides further evidence that the anti-receptor antibody is indeed pathogenic. This past decade has led to a new understanding of this disease, and I suspect we have only begun to "scratch the surface". Hopefully as progress is made, new, more effective, and less toxic approaches to therapy will be found.

References

1. Hide M, Francis DM, Grattan CE, *et al.*: Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med* 1993, 328:1597-1604.