

Urticaria: causes and treatment

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SUMMARY

Chronic urticaria, with or without angioedema, is of unknown aetiology in the great majority of cases. We have recently demonstrated the presence of circulating histamine releasing immunoreactants in 30-50 per cent of patients. That in most of these patients the immunoreactants turned out to be IgG auto antibodies against the high affinity IgE receptor (FcεRI) or, less commonly, IgE itself, was confirmed by chromatography using protein G columns, by immunoblotting and by ELISA as demonstrated in our own and other centres. These auto antibodies are functional since besides releasing histamine from mast cells and basophils, they cause whealing in human skin and their titre shows positive correlation with disease activity. Accordingly, severely disabled patients, unresponsive to routine antihistamines, have been successfully treated by cyclosporin, intravenous immunoglobulin and plasmapheresis. The clinical diagnosis of auto immune chronic urticaria which is clinically indistinguishable from non autoimmune urticaria is therefore of considerable importance and may be aided by enumeration of blood basophil leucocytes and measurement of the serum IgE in patients with chronic urticaria. More recently we have also identified a small subset of patients with chronic urticaria in whom a circulating histamine releasing factor can also be demonstrated but which is only active against mast cells, showing no activity against basophils. This « mast cell specific factor », which is not an immunoglobulin and does not act *via* FcεRI, is currently being characterised.

KEY-WORDS: Urticaria. – Histamine release.

RÉSUMÉ

Urticaire : causes et traitement. – L'étiologie de l'urticaire chronique, avec ou sans angio-œdème, reste inconnue dans la grande majorité des cas. Nous avons récemment démontré la présence de facteurs immunologiques histamino-libérateurs chez 30 à 50 % des patients. Que, chez la plupart de ces patients le facteur immunologique se soit trouvé être des auto-anticorps IgG contre le récepteur IgE de haute affinité (FcεRI) ou, moins souvent, l'IgE elle-même, fut confirmé par la chromatographie sur colonnes de protéine G, par l'immunoblotting et par ELISA, comme cela fut démontré dans notre centre et dans d'autres. Ces auto-anticorps sont fonctionnels puisque, non seulement ils libèrent de l'histamine à partir des mastocytes et basophiles, mais encore ils provoquent une papule sur la peau de l'homme et que leur taux est positivement corrélé avec l'activité de l'affection. Et c'est ainsi que des patients sévèrement atteints, résistant aux antihistaminiques usuels, ont pu être traités avec succès par la cyclosporine, l'immunoglobuline intraveineuse et la plasmaphérèse. Le diagnostic clinique de l'urticaire chronique auto-immune qu'il est impossible de distinguer cliniquement de l'urticaire non immune est donc d'une importance considérable et peut être conforté par la numération des basophiles sanguins et le dosage des IgE sériques des patients atteints d'urticaire chronique. Plus récemment nous avons aussi identifié un petit sous-groupe de patients souffrant d'urticaire chronique chez lesquels peut être démontré la circulation d'un facteur histamino-libérateur, mais actif seulement sur les mastocytes, inactif sur les basophiles. Ce « facteur spécifique des mastocytes », qui n'est pas une immunoglobuline et n'agit pas *via* le FcεRI est en cours d'identification.

MOTS-CLÉS: Urticaire. – Facteurs histamino-libérateurs.

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Chronic urticaria is associated with angioedema in 50 per cent of cases. It is common; about half a million of the U.K's population of fifty-five million will have urticaria at some stage in their lives, and there are about 12,000 new cases per annum. It is extremely disabling; we have shown its handicap to be at least equal to that of patients with triple coronary artery disease awaiting bypass surgery. Its causation defies explanation in the majority of cases. We see about 600 new patients annually in our urticaria clinic at St John's Institute and are rarely able to implicate infections (including *H. pylori*), food additives or «pseudoallergens», parasite infestations or «stress» as causative factors. However, we know that the disease is driven by unwanted cutaneous mast cell degranulation leading to release of histamine and other mediators. What causes this vicarious mast cell stimulation and secretion?

Mast cells can be activated via several mechanisms. These include non-receptor mediated pathways (calcium ionophores) or receptor mediated pathways represented by the mast cell activating action of substance P, nerve growth factor, vasoactive intestinal peptide and other ligands. However, the best known receptor for mast cell activation, also expressed on basophil leucocytes, is the high affinity IgE receptor FcεRI. In this case, specific antigen indirectly cross links adjacent receptors via specific IgE (dimerisation) leading to histamine secretion. This simple mechanism explains acute allergic urticaria satisfactorily. However, we have produced evidence that in some patients with chronic urticaria, IgG directed against the external (alpha-peptide) portion of FcεRI can directly cross link adjacent receptors leading to mast cell activation without the intervention of IgE. This observation is based upon characterisation of histamine releasing activity in the peripheral blood of a subset of chronic urticaria patients. This activity which causes whealing in the uninvolved skin of the donor chronic urticaria patients (autologous serum intradermal test) turned out, on affinity chromatography, to be an IgG with a specificity for the alpha-chain of FcεRI. It released histamine from both normal donor basophils and mast cells. This subset of chronic urticaria patients, representing about 25 per cent of the total, have an auto-immune disease due to functional anti-FcεRIα auto antibodies. These patients have been demonstrated by us to show a high prevalence of certain HLA class II - DR and DQ alleles and to represent a new category of auto-immune disease. In this case (unlike myasthenia gravis in which IgG anti-acetylcholine receptor alpha chain auto-antibodies have a dysfunctional action on the receptor

causing muscular weakness) anti-FcεRIα auto-antibodies promiscuously activate the normal histamine releasing function of cutaneous mast cells leading to whealing and itching. These findings have been confirmed independently by a number of different groups which have identified anti FcεRIα auto-antibodies in about 33-60 per cent of their patients with chronic urticaria and angioedema. Anti-FcεRIα auto-antibodies are not found in healthy individuals, patients with psoriasis, asthma, atopic dermatitis or physical urticarias. However, nonfunctional (i.e. non-histamine - releasing) anti-FcεRIα auto-antibodies have been identified in a few patients with dermatomyositis and pemphigus vulgaris.

We have also identified a further small subset of chronic urticaria patients, representing about five per cent of the total, who have IgG anti-IgE auto-antibodies. In these patients, cross-linking of FcεRIα occurs via IgE due to binding of a single IgG anti-IgE via its Fab portion to the Fc segment of adjacent IgE molecules. These auto-antibodies are probably also functional and therefore pathogenic (fig. 1).

Diagnosis of auto-immune urticaria still relies in our laboratory on a positive autologous serum test followed by *in vitro* demonstration of histamine release from normal donor basophils. Immunoassays and flow cytophot assay utilising for FcεRIα auto-antibodies are currently under development.

The finding of a substantial subset of patients with chronic urticaria in which autoimmunity plays a major role has prompted exploration of immunotherapy in severely affected patients unresponsive to conventional treatment. We have recently reported the successful use of plasmapheresis and IVIG. Cyclosporin is also effective but works equally well in auto-antibody positive and - negative patients. Epitope mapping in the hope of developing structure-based peptides for use (after humanisation) as a specific form of immunotherapy is currently being explored.

Recently we have identified a further subset of chronic urticaria patients with a novel mast cell - specific histamine releasing factor. This factor causes whealing in human skin, releases histamine from mast cells of normal healthy donors but does not release from basophils. It is not an immunoglobulin and does not act via FcεRIα. It does not appear to release histamine via known receptors expressed by mast cells. It has been found in at least 12 per cent of our patients with chronic urticaria. Its presence has been independently confirmed by at least one other group. This activity is awaiting full characterisation.

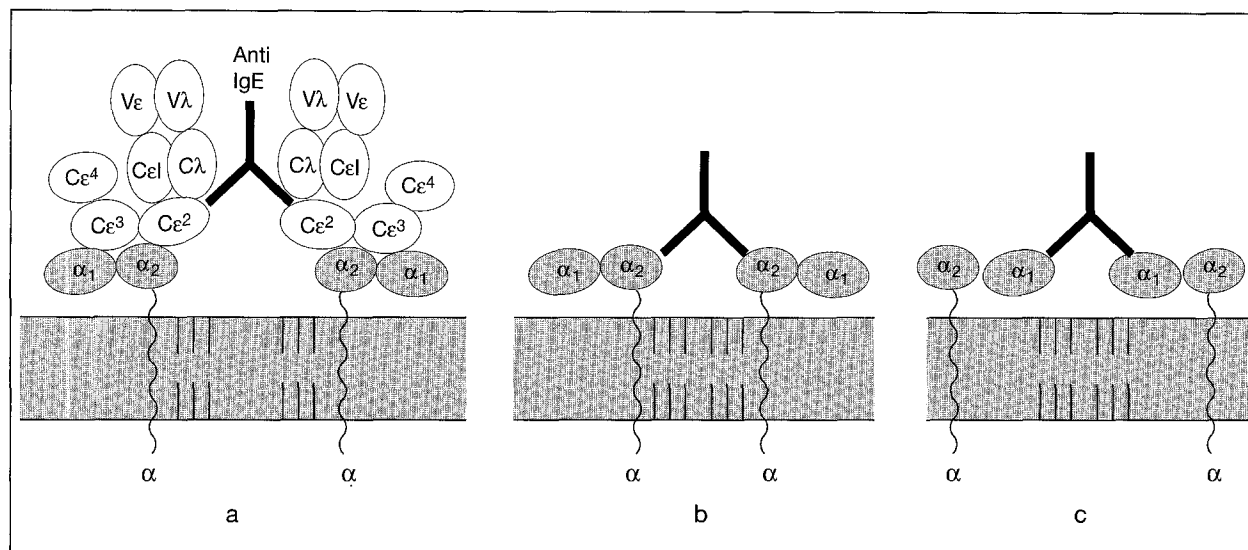


Fig 1. – Autoimmune urticaria: anti-FcεRIα and anti-IgE auto antibodies. a) IgG-anti-IgE autoantibody (Type IA chronic urticaria). b) IgG-anti-FcεRIα autoantibody (Type I chronic urticaria). This autoantibody binds the α₂ domain of FcεRIα and is therefore competitive with IgE. c) IgG-anti-FcεRIα autoantibody (Type I chronic urticaria). This autoantibody does not bind to the α₂ domain and is not competitive with IgE. Epitope mapping to precisely identify the binding site for anti-FcεRIα autoantibodies is in progress.

We are left with about 18 per cent of patients with chronic urticaria who appear to have a wheal producing factor (they have a positive autologous serum skin test) but their serum releases no histamine from mast cells on basophils of normal donors. It may be that histamine releasing activity could be confirmed in these sera if a larger panel of donor basophils or mast cells was used, or if the sensitivity of the *in vitro* histamine release assay was enhanced by pre-treatment with IL-3 deuterium oxide or pre-incubation with hr alpha peptide as suggested by some authors. There are also the remaining 40 per cent of chronic urticaria patients with a negative autologous serum skin test. A few of these may be intolerant of food additives or «pseudo allergens» although in our hands, utilising placebo controlled single blind challenge testing, these represent less than 5 per cent of the total. The cause of the whealing in the remainder continues to be enigmatic.

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