

Viewpoint

Not all chronic urticaria is “idiopathic”!

Greaves MW, O'Donnell BF. Not all chronic urticaria is “idiopathic”!
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Abstract: The aetiology of chronic urticaria in the majority of patients is elusive. The cause of physical urticarias (dermographism, delayed pressure urticaria, cold urticaria) is unknown. We have identified a subset of chronic “idiopathic” urticaria patients, representing approximately 30% of the total in which the disease is caused by the presence of IgG autoantibodies against the high affinity IgE receptor (FcεRIα). This functional autoantibody stimulates normal (albeit vicarious) activation of mast cells and basophils via FcεRI, causing whealing and angioedema. Anti-FcεRI-positive patients are recognized by a combination of autologous serum skin testing and evoked histamine release from basophils of normal human donors. Autoantibody-positive and -negative patients are clinically indistinguishable and are treated routinely by combinations of H₁ and occasionally H₂-antihistamines in both cases. However, severely affected patients who are anti-FcεRI-positive can also be treated by non-specific immunotherapy (plasma pheresis, intravenous immunoglobulin, cyclosporin).

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Of all the “heart sink” diseases of the skin, chronic urticaria is one of the most greatly feared, causing enormous distress and frustration to patient and physician alike. It is very common, and the best figures available suggest that around half a million of the fifty-five million population of the UK will suffer chronic urticaria at some point in their lives (1). It is also extremely disabling. We have recently reported that the degree of personal, social and occupational disability (assessed by an internationally recognized “quality of life” formula) is of the same order as that of patients with severe triple coronary artery disease awaiting surgery (2).

Inspection of current editions of dermatology and allergy text books lists a range of causes, including chronic infections (*Helicobacter pylori* is the current favourite), infestations, food allergies and idiosyncratic reactions and “stress”. In over 20 years' experience in running a very busy urticaria clinic at St John's Institute of Dermatology (we see upwards of 500–600 new patients annually), we do not recognize these as major causes. Even with food additives, if strict criteria are applied – we believe the gold standard must be a demonstration of *reproducible* placebo controlled challenge test response – only a handful of proven food additive reactors emerge as culprits each year. What then does cause chronic “idiopathic” urticaria?

To answer this, we went back to the basic lesion of chronic urticaria – the itchy wheal. This is caused by degranulation of dermal mast cells, with consequent secretion of histamine and other mediators leading to redness oedema and a flare (the “Triple Response” of Lewis) and itching. Mast cells can be triggered to degranulate in a number of ways, most of which involve specific cell-surface receptors. The best known of these, the high affinity IgE receptor (called FcεRI for short), binds immunoglobulin E which in the skin is responsible for acute urticaria. In other words, if someone is acutely allergic to, say, penicillin, then inadvertent ingestion of penicillin allows the penicillin antigen to combine with penicillin-specific IgE, leading to cross-linking of adjacent FcεRI via IgE (panel A of Fig. 1). What we have recently demonstrated is that at least 30% of chronic urticaria patients have an IgG autoantibody (IgG anti-FcεRI), which directly cross-links adjacent FcεRI on the surface of the skin mast cell (panel B of Fig. 1), triggering release of histamine and other mediators and causing the itchy wheals which are so familiar in chronic urticaria (3, 4). Our findings have been independently confirmed by several groups in Europe and the US (5, 6). Indeed, American workers claim autoantibodies are causative in as many as 60% of their patients (6).

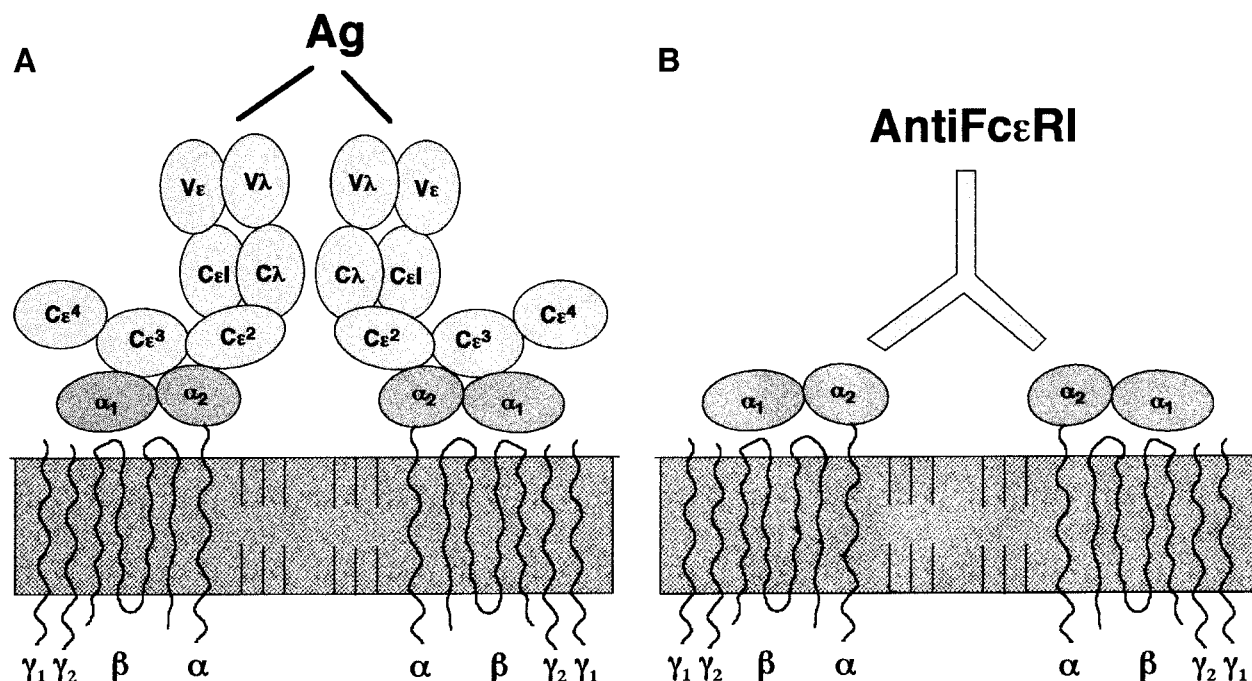


Figure 1. (A) Antigen cross-links the high affinity IgE receptor (FcεRI) via specific IgG. (B) Autoimmune chronic urticaria: anti-FcεRI IgG cross-links FcεRI directly via alpha subunit. Ag: antigen; V: variable region; C: constant origin; γ₁, γ₂, β and α represent four peptide chains of FcεRI.

These IgG autoantibodies are functional (rather than irrelevant immunological bystanders). We know this for the following reasons: i) when reinjected back into the patient's own skin they cause whealing (see later); ii) they release histamine from human skin mast cells *in vitro* (7); iii) removal of these autoantibodies by plasmapheresis (8) (see later) causes clinical remission. Are we dealing with a novel autoimmune disease in this large subset of patients with chronic urticaria? Fundamental criteria need to be satisfied before a disease can be recognized as autoimmune. We have identified a specific antigen with which the antibody reacts (the alpha-subunit of FcεRI). We have demonstrated passive transfer of the disease both *in vitro* and *in vivo*. Finally, we have demonstrated remission by removal of the antibody.

Therefore, in some patients chronic urticaria is due to anti-FcεRI autoantibodies and in these, it represents an autoimmune disease.

It is noteworthy that autoimmune diseases due to functional autoantibodies against receptors are well recognized – examples include autoantibodies against the alpha subunit of the acetyl choline receptor in myasthenia gravis, and against the insulin receptor in certain types of insulin resistance. However, in these instances the autoantibodies cause perturbation of the normal function of the receptor. In contrast in the case of autoimmune chronic urti-

caria, the IgG autoantibody combines with the alpha subunit of the high affinity IgE receptor leading to elicitation of its normal (albeit in the context vicarious) function – mast cell activation and release of mediators, leading to whealing and itching. For an autoantibody to initiate “normal” function of a receptor is almost unique – the only other recognized example being thyrotoxicosis in which overproduction of thyroxine is a result of the action of an IgG auto antibody against the thyroid stimulating hormone receptor (TSHr), expressed by thyroid parenchyma cells.

How is this important autoimmune subset of chronic urticaria recognized in practice? We are unable to identify any distinguishing clinical features. Although there is no evidence of urticaria vasculitis, we are currently carrying out histological studies of skin biopsy material in case there are distinguishing cytological features. At present, patients are screened by carrying out an autologous serum intradermal skin test in which the patient's serum is injected back into his or her own skin; the presence or absence of whealing indicating the presence of a wheal-producing factor. The serum is also examined for histamine releasing activity against basophil leukocytes from healthy donors. An immunoassay is currently under development. Clearly these procedures are appropriately carried out by a specialist unit.

The identification of this subset of chronic urticaria is of great practical importance, since we have shown the favourable response of autoantibody positive patients to immunotherapy by cyclosporin (9), intravenous immunoglobulin (IVIG) (10), and plasmapheresis (8). These measures, which cause remission but are not curative, are only offered to autoantibody positive patients who suffer severe social occupational or personal disability as a result of their disease. The routine treatment for chronic urticaria (whether autoimmune or not), remains judicious use of combinations of H₁ antihistamines.

Looking to the future, epitope mapping of the alpha subunit, to detect peptide sequences with which the anti FcεRI autoantibody reacts should enable development of structure-based peptides, and offer the possibility of selective immunotherapy for these severely affected individuals, many of whom suffer from chronic toxicity due to systemic steroid treatment.

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