

Autoantibodies to the high-affinity IgE receptor in chronic urticaria: how important are they?

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Purpose of review

Eighty to 90% of patients with chronic urticaria have no specific external cause for their disease, which is therefore labeled 'chronic idiopathic urticaria'. We now know, however, that as many as 30–50% of patients have evidence of an autoantibody to the high-affinity receptor for IgE (FcεRI), which may be pathogenic. The exact prevalence and role of these autoantibodies is still under investigation.

Recent findings

The frequency of autoantibodies to FcεRI in chronic urticaria has been estimated at 30–50%, but extensive epidemiological studies have not been done. Recent work has confirmed that autoantibodies to FcεRI can be functional, meaning that they can cause histamine release from basophils *in vitro*. Evidence increasingly suggests that such autoantibodies are also functional *in vivo*, but conclusive evidence is still lacking. Approximately 50% of cases of urticaria still have no known cause, but recent studies have demonstrated that some of these patients may have intrinsic abnormalities of basophils or mast cells.

Summary

The recent evidence that is discussed in this review helps to clarify the role of autoantibodies in some cases of urticaria, but also points towards other non-autoimmune mechanisms that might be pathogenic. Further investigation in these areas will help us to understand the cause of urticaria in cases that are still classified as 'idiopathic'.

Keywords

autoimmune, basophil, chronic urticaria, FcεRI, mast cell

Introduction

Urticaria is a heterogeneous condition. There are a number of potential causes, and the severity and clinical pattern can vary considerably from patient to patient. Urticaria is considered to be chronic when symptoms have been continuously or intermittently present for at least 6 weeks [1]. At least 80–90% of patients with chronic urticaria are found to have no external cause of their condition, that is, they do not have a physical, food, topical allergen, or drug induced condition. These patients are traditionally referred to as having 'chronic idiopathic urticaria'. There is now considerable evidence that up to 30–50% of patients with chronic urticaria have autoantibodies to the α-chain of the high affinity receptor for IgE (FcεRI) [2]. It is thought that these autoantibodies are present in the circulation of these patients, and lead to the activation of infiltrating basophils or skin mast cells, thereby causing hives (although conclusive evidence of this mechanism is still lacking). Therefore, a good proportion of 'chronic idiopathic urticaria' is thought to be an intrinsic autoimmune condition. Further evidence supporting an autoimmune basis for urticaria in some patients is the close association with thyroid autoimmunity, which is a discussion that is beyond the scope of this review. Chronic urticaria patients without autoantibodies still have no clear cause for their urticaria, but recent evidence suggests that a population of patients has intrinsic basophil or mast cell defects which may be the underlying cause of hives in these patients.

Evidence of the presence, prevalence and functionality of autoantibodies to the high-affinity IgE receptor (FcεRI)

From the mid-1980s onwards, investigators have been able to demonstrate that intradermal injection of autologous serum causes an immediate wheal and flare response in some patients with chronic urticaria [3], and that this process seems to occur only during disease activity but not remission [4,5]. This intradermal injection of serum is now often used diagnostically, and is referred to as the 'autologous serum skin test' [3]. Further evidence demonstrated that many of these patients appeared to have circulating serum 'histamine releasing factors', meaning that the serum from these patients was able to cause histamine release from donor basophils when the basophils were incubated in the patient's serum [3,6,7]. This *in-vitro* histamine release also occurred with purified IgG fractions of the serum in the majority of

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Abbreviation

ELISA enzyme-linked immunosorbent assay

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patients, suggesting that the histamine releasing factor in most cases was an IgG antibody [6,8]. Inhibition or immunoblotting experiments demonstrated that the histamine releasing IgG antibody appeared to be an autoantibody to the α -chain of the high-affinity IgE receptor (Fc ϵ RI) in the majority of such patients [9,10]. The presence of such autoantibodies to Fc ϵ RI that are functional *in vitro* in causing histamine release from donor cells has been confirmed by many authors, and the activity of such autoantibodies continues to be further characterized. Recently it was found that the histamine releasing activity of sera on donor basophils could be blocked by pre-incubating the basophils with the calcineurin inhibitors cyclosporin and ascomycin [11[•]]. Interestingly, cyclosporin has demonstrated clinical efficacy in the treatment of the autoimmune form of chronic urticaria [12]. In a small number of cases, the serum with histamine-releasing activity has no evidence of autoantibody to the high-affinity IgE receptor, and in these cases it is thought that the serum may contain autoantibodies to the IgE molecule itself [10,13].

Further evaluation of the nature and functionality of autoantibodies to Fc ϵ RI has shown that the functional activity of the autoantibodies are augmented in the presence of components of the classical complement cascade [14], and the critical component appears to be complement component C5a [15].

There may well be clinical differences between patients with autoantibodies to Fc ϵ RI and those with other mechanisms. Patients with the autoimmune form of chronic urticaria (as established by having a positive 'autologous serum skin test' rather than demonstration of functional autoantibodies *in vitro*) appear to have more severe urticaria [16[•]] and a longer duration of disease [17[•]].

Recent studies have continued to suggest that up to 30–50% of patients with chronic urticaria have autoantibodies to the high-affinity IgE receptor. These studies have generally been done at specialized centers for urticaria (which likely follow a population of patients with much greater disease severity than the general urticaria population); therefore, this high rate of prevalence may be overestimated due to selection and referral bias. The prevalence of such autoantibodies in a general population of patients with all severities of urticaria may be similar but may be lower. More detailed epidemiological studies are needed to determine the exact prevalence of autoantibodies to Fc ϵ RI in urticaria patients overall.

Because of the considerable evidence that the serum from many patients with chronic urticaria can cause an immediate autologous wheal and flare response (i.e. a positive 'autologous serum skin test'), and that many of

these patients have evidence of circulating functional IgG autoantibodies to the high-affinity IgE receptor, Fc ϵ RI, the current mainstream thought is that in such patients the IgG autoantibodies are causing the visible urticarial skin lesions.

Are autoantibodies to Fc ϵ RI exclusive to chronic urticaria, and is measurement of these autoantibodies specific for chronic urticaria?

Autoantibodies have been found in some patients with pemphigus, dermatomyositis, systemic lupus erythematosus, and bullous pemphigoid [18]. The significance of the autoantibodies in these other diseases is unclear, but in these diseases the autoantibodies were of subtypes IgG2 and IgG4, whereas in chronic urticaria the autoantibodies are predominantly IgG1 and IgG3. This difference in subclasses might be significant, as recent work has shown that the subclasses of autoantibody that are functional in causing histamine release are predominantly IgG1 and IgG3, and to a lesser degree IgG4, although this is not absolute and there can be non-functional autoantibodies of these subclass types [19^{••}].

A study [20] found that using enzyme-linked immunosorbent assay (ELISA) and immunoblot techniques, autoantibodies to Fc ϵ RI could be found not only in chronic urticaria patients, but also normal individuals, as well as in units of therapeutic intravenous immunoglobulin (IVIG). The autoantibody in IVIG was not functional in causing histamine release, but interestingly, cross-reacted with tetanus toxoid on immunoblot. The authors speculated that the anti-Fc ϵ RI may belong to the body's natural antibody repertoire, and may serve as the parental antibody for some anti-tetanus toxoid antibodies. They also suggested that there may be heterogeneity of anti-Fc ϵ RI, recognizing different epitopes. This study implies that immunoblot and ELISA for measuring anti-Fc ϵ RI may not be valid techniques (indeed, other studies have found poor correlation between measurements of anti-Fc ϵ RI by immunoblotting versus using a functional histamine release assay [19^{••},21]), but also raises the question as to whether the autoantibodies are truly pathogenic in all cases of chronic urticaria. It does appear that a number of subtypes of anti-Fc ϵ RI appear to be non-functional antibodies. Therefore, use of an immunoblotting or ELISA technique is unlikely to be specific for detecting functional autoantibodies in chronic urticaria, and therefore the 'gold standard' for detecting such autoantibodies is the functional in-vitro donor basophil histamine release assay as discussed previously. The 'autologous serum skin test' has been used as a proxy for the measurement of functional autoantibodies to Fc ϵ RI, but there is concern that there may be both false positive (due to formation of other vasoactive mediators while processing the serum) and false negative (due to degradation of the

histamine releasing factor or autoantibody) results with the skin test. Also, patients with both Hashimoto's thyroiditis and autoimmune urticaria can have a persistence of a positive autologous serum skin test even after the urticaria has resolved, suggesting that something associated with Hashimoto's thyroiditis can lead to a false positive skin test [22^{*}]. On the other hand, it has been argued that what appear to be 'false positive' autologous serum skin test results (where the basophil histamine release assay is negative) may actually point toward patients who have a mast cell-specific serum histamine releasing factor that is not active on basophils [23]. Certainly, more research is needed to establish the sensitivity and specificity of these tests in detecting clinically relevant autoantibodies. The functional basophil histamine release assay (using donor basophils) is a fairly cumbersome and lengthy test to perform. For this reason, attempts have been made to develop other functional basophil assays which are easier and quicker to run. An assay measuring donor basophil expression of CD63 after incubation with patient serum has been reported [24], as well as a similar assay that measures basophil expression of CD203c (which is more specific for basophils) [25], but more data will be needed to determine if these assays are adequately sensitive and specific.

Is there evidence that autoantibodies to FcεRI are functional and pathogenic *in vivo*?

The *in-vitro* studies discussed previously have demonstrated that in many cases, the autoantibodies to FcεRI found in chronic urticaria patients appear to be 'functional', that is, that they are able to cause histamine release when they come into contact with basophils and mast cells in the lab. It is therefore assumed that these antibodies are also functional *in vivo*, and are the cause of the urticarial skin lesions that these patients experience. Clear evidence that this is indeed the case *in vivo* is still lacking. The 'autologous serum skin test' has been used as a proxy for the measurement of functional autoantibodies to FcεRI, and has been suggested as evidence that the autoantibodies are also functional *in vivo* in causing the urticaria, but studies have not shown good correlation of autologous serum skin test results and the presence of functional autoantibodies [23,26]. We need further research to conclusively confirm whether these autoantibodies are truly the cause of hives in patients who have them.

Evidence of other potentially pathogenic abnormalities in chronic urticaria

The 50–70% of patients who do not have autoantibodies to FcεRI still often have no identifiable cause for their hives. There is increasing evidence that there may be abnormalities in number, structure or function of basophils or mast cells in patients with chronic urticaria. These abnormalities may be independent of

the presence of autoantibodies to FcεRI. Whether these other abnormalities may be pathogenic in the disease process is not yet clear.

Patients with chronic urticaria and autoantibodies to FcεRI have been found to have lower circulating basophil counts [7], and basophils that are hyporesponsive to non-specific stimulation through FcεRI [7,27]. This finding suggests that some chronic urticaria patients may have a population of functionally distinct basophils, or basophils that are somehow desensitized through the FcεRI pathway. Furthermore, chronic urticaria patients with histamine-releasing serum activity have lower basophil counts than chronic urticaria patients without releasing activity [28]. A recent study [29^{**}] found that basophils from both patients with autoimmune as well as non-autoimmune chronic urticaria were hyporesponsive to non-specific stimulation with anti-IgE and C5a, but interestingly were hyperresponsive to sera from other chronic urticaria patients and even normal sera. Therefore, it appears from this study that basophils from chronic urticaria patients can be functionally abnormal, showing hyporesponsiveness to some stimuli but hyperresponsiveness to something contained in both patient and normal sera.

There has been considerable recent exploration of possible specific intrinsic basophil or mast cell defects in chronic urticaria patients. In one small study [27], an increase in SHIP-1 and SHIP-2 proteins was noted in basophils of certain chronic urticaria patients, and an altered form of SHIP-2 was found in certain chronic urticaria and cold urticaria patients [27]. SHIP-1 and SHIP-2 are known to be negative regulators of signaling through FcεRI. This study suggested that certain chronic urticaria patients may have altered basophil FcεRI signaling. Another small study [30] found increased levels of activation markers (CD63, CD69 and CD203) of basophils of chronic urticaria patients compared with allergic participants. There continues to be accumulating evidence that the basophils of some chronic urticaria patients are hypo-responsive to non-specific stimuli to FcεRI. Preliminary work suggests that a proportion of patients with non-responsive basophils appear to have deficiency of Syk kinase (a positive regulator of signaling through FcεRI) [31]. Preliminary evidence also suggests that there may be differences in basophil signaling between those patients who have basophils that are responsive to non-specific stimuli and those who have non-responsive basophils [32]. This area of investigation will likely receive further attention in upcoming years. It may turn out that basophil or mast cell signaling defects may be the causative factor in a subgroup of patients with chronic urticaria, with abnormal signaling leading to spontaneous hives. This may explain 'chronic idiopathic urticaria' in a number of the patients who do not appear to

have autoantibodies to FcεRI. Other chronic urticaria patients may have cellular signaling defects in addition to autoantibodies to FcεRI. In these patients, further research will be needed to determine which of the two abnormalities (if not both) is causative of the urticaria.

Conclusion

We now have substantial evidence that some patients with chronic urticaria have autoantibodies to FcεRI which are functional *in vitro* in causing histamine release from donor basophils. Studies have estimated that 30–50% of chronic urticaria patients have such autoantibodies, but these studies have generally been done in highly specific populations of patients seen at tertiary referral centers. Therefore, the true prevalence in urticaria overall is still unknown, but may be somewhat lower. Since autoantibodies to FcεRI are functional *in vitro*, it makes sense that they would also have the potential to cause skin lesions in the patient, but specific studies to confirm in-vivo activity have not been done. Such studies will likely be difficult to perform given ethical considerations with performing in-vivo intradermal injections with any non-autologous or altered substances. In the meantime, the best evidence that we have to indicate that autoantibodies to FcεRI cause skin lesions is the presence of a positive autologous serum skin test in many of these patients. Studies have not always shown good correlation, however, between the autologous serum skin test result and in-vitro histamine releasing activity.

Recent studies have uncovered abnormalities in number and function of basophils in patients with chronic urticaria, and there may also be functional abnormalities of skin mast cells. These abnormalities may account for the urticaria in some of the remaining patients who are still currently classified as having 'chronic idiopathic urticaria'.

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