

Review article

Factors responsible for differences between asymptomatic subjects and patients presenting an IgE sensitization to allergens.

A GA²LEN project

The synthesis of allergen-specific IgE is required for the development of allergic diseases including allergic rhinitis and allergic asthma (patients), but many individuals with allergen-specific IgE do not develop symptoms (asymptomatic subjects). Differences may exist between asymptomatic subjects and patients. Whether the presence of allergen-specific IgE translates into clinical allergy most likely depends on a complex interplay of multiple factors. These include a family history of atopy, the levels of total serum IgE and, allergen-specific IgE or IgG, epitope-specificity of IgE and their degree of polyclonality (mono- vs polysensitized), as yet unidentified serum factors, the balance of T regulatory cells (Treg) and Th1/Th2 cells, the polymorphisms of the high affinity receptor for IgE (FcεRI) and other factors regulating the activation of FcεRI-bearing cells. Asymptomatic subjects may be more often monosensitized than patients who may be more often polysensitized. There are many unanswered important questions that need to be addressed in order to better understand how IgE sensitization translates into clinical allergy. The assessment of differences between the asymptomatic and symptomatic groups of subjects represent one of the scientific programs of Global Allergy and Asthma European Network funded by the European Union and the hypotheses underlying these differences are presented in this paper.

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Abbreviations: ECRHS, European Community Respiratory Health Subject; FcγRIIB, low affinity receptor for IgG; FcεRI, high affinity receptor for IgE; GA²LEN, Global Allergy and Asthma European Network; Th1, T helper cell type 1; Th2, T helper cell type 2; Treg, T regulatory cell.

The synthesis of IgE against allergens is required for the development of allergic diseases including allergic rhinitis and allergic asthma (1), but many individuals with allergen-specific IgE do not develop symptoms.

Serum allergen-specific IgE or positive skin tests to common aeroallergens are observed in asymptomatic subjects (2–8). Using passive transfer tests, it was shown that these antibodies were functional (2, 3) In the Dutch European Community Respiratory Health Subject (EC-RHS) study, 43% of the subjects with IgE to inhalant allergens did not present respiratory symptoms (8). In longitudinal studies, the presence of positive skin tests in nonsymptomatic subjects predicts the onset of allergic symptoms including asthma (9–12).

There are many important questions which need to be addressed to better understand the reasons why some IgE-sensitized subjects do not develop allergic symptoms. The assessment of differences between the two groups of subjects represent one the scientific programs of Global Allergy and Asthma European Network (GA²LEN) funded by the European Union and the hypotheses underlying these differences are presented in this paper.

Family history of atopy

Although a family history is insufficient to identify the atopic constitution (1), the family history of atopy may differ between asymptomatic subjects and patients. In the prospective birth MAS, it has been found that many asymptomatic subjects were born from nonatopic families (13). In the ECRHS study, over 80% of subjects with allergen-specific IgE and a family history of atopy had allergic respiratory symptoms whereas only around 65% of subjects without a family history of atopy presented with symptoms of respiratory allergy (Leynaert, Neuhirch, Bousquet, personal communication). In the same ECRHS study, there were geographic variations in the effect of atopy on asthma (14).

Mono and polysensitization against allergens

The discrimination between mono- and polysensitized subjects is optimally achieved using purified natural or recombinant allergens (15, 16). New techniques for the determination of IgE reactivity profiles using microarrays will also improve the characterization of allergic sensitization (17).

Exposed to a common environment, the IgE-mediated immune response differs among sensitized subjects, some of them react towards a limited number of allergens (mono or pauci-sensitized) whereas others are sensitized to a wide array of allergens (polysensitized). Pepys categorized atopic status into 0, 1, 2 or 3 or more groups according to the number of positive skin prick tests to a small battery of relevant allergens (pollens, house dust mites, cat and a locally important mold allergen) (18, 19). Taking into consideration cross-reactivities between

allergens and panallergens (20), a minority of symptomatic patients is sensitized to a single allergen (monosensitized) whereas over 75% present IgE against several allergens (polysensitized) (Fig. 1).

Mono- and polysensitized patients may differ in terms of their immune response. By comparison with polysensitized patients, monosensitized ones usually have lower serum total IgE levels (21, 22), lower serum allergen-specific IgE levels (22, 23), a reduced Th2 cytokine release from peripheral blood mononuclear cells after nonspecific stimuli (24, 25) and allergens (23). Outside of the pollen season, only polysensitized patients have a Th2 cytokine production after pollen challenge (23). In grass pollen allergy, monosensitized patients usually react to one or two allergenic proteins of orchard grass pollen whereas polysensitized patients have IgE against a large number of them (26).

HLA plays a role in the development of the IgE response to the allergens, but genetic regulation appears to differ in mono- and polysensitized patients. Associations between HLA haplotypes or HLA-DQ/DR molecules and allergen sensitivity were confirmed only in patients either with low total serum IgE levels or monosensitized (27–31). In low-IgE responder patients (low total IgE or monosensitized) the allergic sensitization depends more closely on HLA-DR or DQ molecules than in patients with high total IgE or polysensitized (32, 33). In another study, the *Parietaria* IgE antibody response was associated with DRB1*1104 in patients with low total IgE and with DRB1*1101 in patients with high total IgE (34). HLA-DR4 is a protective class II antigen against sensitivity to Ole e 1, the major antigen of olive pollen, and HLA-DQ2 is a risk factor for it (35).

Monosensitized patients appear to be either children who may develop polysensitization later in life or adults who will only develop a single allergenic sensitivity (22, 36, 37). The onset of symptoms in monosensitized tree

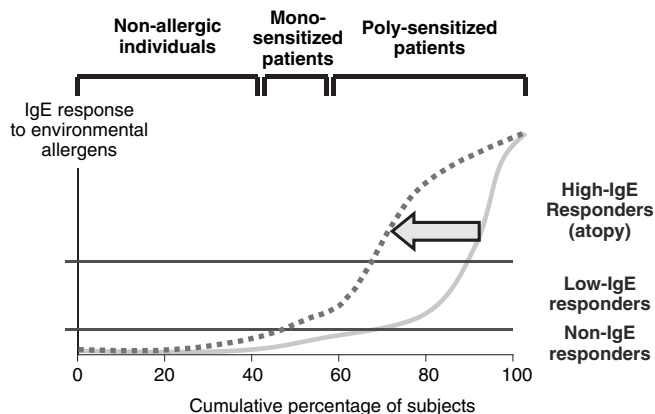


Figure 1. Relative distribution of non-allergic and allergic individuals before (—) and during (---) the 'allergy epidemic' (←⇒).

pollen allergic patients often occurs in adult life (22, G. Passalacqua and C. Lombardi, unpublished observation).

These considerations suggest that monosensitized patients may belong to an intermediate group between nonatopic and fully atopic individuals (22, 38, 39).

Levels of allergen-specific IgE

Asymptomatic subjects have lower serum allergen-specific IgE levels than symptomatic patients for inhalant (5, 8, 40) and food allergens (41–45). Skin test results but not serum IgE reflect immediate type respiratory sensitivity (46). Moreover, skin test reactivity to inhalant allergens is reduced in asymptomatic subjects when compared with symptomatic patients (5). However, despite the overall trend of a correlation between the degree of IgE sensitization and the risk for allergic symptoms, IgE thresholds are far from being absolute.

Qualitative differences in allergen-specific IgE

Qualitative differences in IgE may occur and suggest that not all IgE are equally effective in activating high affinity receptor for IgE (FcεRI). Several splice variants of the secreted human ε heavy chain have previously been identified and may have a different functional activity (47). Avidity of IgE differs (48) and a differential expression of IgE isoforms and changes in the fine specificity of the IgE response have been observed (49). For efficient mediator release, the number of epitopes recognized on an allergen (epitope-valency) and the avidity of the interaction between IgE and the allergen are decisive (50). Poor biological activity has often been reported in relation to IgE cross-reactivity between different allergen sources (e.g. between inhalant and food allergens) (51, 52).

Allergen molecules with high and low allergenic activity

Allergens with low IgE-binding capacities can induce strong allergic reactions whereas allergens with strong IgE binding capacity are sometimes less able to do so (46). At the molecular level, the concentration of allergen-specific IgE capable of binding to the FcεRI is not necessarily associated with biological sensitivities, and a moderate association was found between cutaneous and basophil sensitivities (53). It is therefore possible that allergen molecules may have high and low allergenic activities.

Levels of allergen-specific IgG and IgA

The relationships between IgE and IgG₄ have been studied both in parasitic and allergic diseases (54). For some allergens (e.g. mite and cockroach), the prevalence of sensitization appears to be directly correlated with expo-

sure (55, 56). For domestic animal allergens, some studies have suggested that children with a cat in the home have a decreased risk of sensitization and asthma, whereas others suggested that early exposure may increase the risk of allergic sensitization (57–60). Many children exposed to high levels of Fel d 1 in dusts made an IgG and IgG₄ response to Fel d 1 without IgE antibody (61). This modified Th2 response is not associated with symptoms and may be regarded as a form of immunological deviation (62). Allergen-specific IgG may act as a blocking antibody (63, 64). The increase in serum specific IgA and IgG₄ concentrations coincides with increased TGF-β and IL-10 produced by blood mononuclear cells (65). However, it appears that allergic patients form IgA antibodies against many pollen proteins but not against allergens (66).

Levels of total IgE

Epidemiologic studies in parasitic infections have suggested a protective role of high total IgE titers against IgE-mediated symptoms (67–72). High titers of IgE may saturate FcεRI, thereby preventing sufficient occupancy of receptors with allergen-specific IgE. This effect can be demonstrated in *in vitro* basophil histamine release experiments (R. Van Ree, personal communication). However, more recent studies have not found an inverse correlation between high IgE and biological activity of specific IgE (73, 74) possibly because earlier studies did not take confounding factors such as age, sex, nutrition, and socioeconomic factors into account. Another argument against the proposed saturation of FcεRI with polyclonal IgE is supported by clinical trials with anti-IgE (75).

T-cell regulation

It is possible to find T cells reactive to allergenic peptides in patients with and without significant levels of IgE against the allergens. The T-cell recognition of the allergen epitopes may not differ in subjects with or without allergen-specific IgE (76–78).

The regulation of the IgE immune response by Th2-/Th1-cell balance has been demonstrated in allergic diseases. However, the suppressive role of T regulatory cells (Treg) in allergy has been investigated recently. Several types of CD4⁺ Treg cells have been described (79, 80).

Immune responses in healthy and allergic individuals appear to be characterized by a fine balance between allergen-specific Treg and Th2 cells (81–83). Th2-cytokine suppression by CD4⁺CD25⁺ Treg cells is reduced in atopic individuals, and particularly so during the pollen season (83, 84). In children who have outgrown cow's milk allergy, mucosal induction of tolerance against dietary antigens is associated with the development of allergen-responsive CD4⁺CD25⁺ Treg cells (85).

CD8-Der p1-specific T cells from house dust mite sensitized individuals produce IFN-γ efficiently, but their

IL-10 production is significantly reduced in symptomatic patients by comparison with asymptomatic subjects (86).

It is therefore possible that asymptomatic subjects and patients differ in the expression of Treg cells, especially those releasing IL-10 as this cytokine is known to reduce basophil and mast cell mediator release (87).

Polymorphism of the FcεRI

Many genetic factors may be involved in the differences between asymptomatic subjects and patients, but the polymorphism of the FcεRI may be one the most relevant even though it has not been tested in asymptomatic subjects with IgE sensitization. The gene for the FcεRIβ-chain has been proposed as a candidate gene for atopy. Some pedigree studies of atopy and asthma have suggested linkage with the FcεRIβ gene on chromosome 11q13, but others find no linkage (88–95).

Negative signals in cells bearing FcεRI

Human mast cells and basophils that express FcεRI have key roles in allergic diseases (96). However, there are regulatory mechanisms explaining why some subjects with allergen-specific IgE do not present symptoms when exposed to the relevant allergens (97–101) (Fig. 2).

There are several reasons explaining the down regulation of FcεRI-bearing cells. In asymptomatic sensitized subjects, the low level of allergen-specific IgE (i) may down-regulate FcεRI on basophils and mast cells (75, 102), (ii) may not induce mast cell activation and release of mediators and cytokines, and (iii) may reduce basophil survival directly or indirectly (103).

Another possible explanation is the occurrence of allergen immune complex with IgG. Mast cells and basophils co-express low affinity receptor for IgG (FcγRIIB) (104), a low affinity receptor containing an immunoreceptor tyrosine-based inhibitory motive (ITIM) and whose co-aggregation with FcεRI can, *in vitro*, block FcεRI-mediated reactivity (105–108). FcγRIIB-deficient mice are hypersensitive to anaphylactic reactions (109, 110) supporting the *in vitro* findings. In addition, recent reports suggest that the p110δ isoform of PI(3)K importantly contributes to mast cell activation downstream of FcεRI. Inactivation of p110δ protects mice

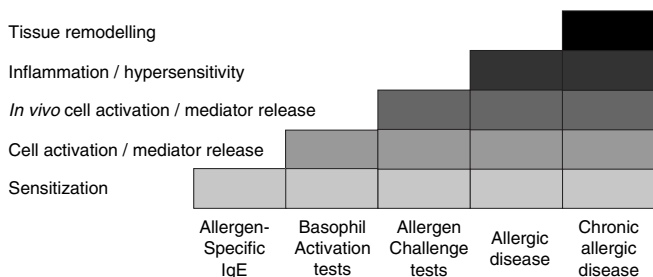


Figure 2. From allergen-specific IgE to IgE-mediated disease.

against anaphylactic allergic responses (111). However, data obtained in rodent models may not be directly translatable to the human (112).

Basophils and mast cells may not be the only cells involved in this down-regulation. On monocytes and antigen presenting cells the intensity of surface expression of FcεRI is positively associated with the atopic status of the individual (113, 114). Lower levels of IgE may down-regulate FcεRI expression on dendritic cells (115) and FcεRI-FcγRII co-aggregation inhibits IL-16 production from human Langerhans-like dendritic cells (116). Moreover, FcεRI is reduced in atopic subjects who are asymptomatic at the time of the study (117).

Impact of bacterial superantigens

Staphylococcus aureus, besides its infectious properties, produces several toxins with superantigenic properties (118). *Staphylococcus aureus* superantigens may influence the activity of both immuno-modulatory and pro-inflammatory effector cells (119). They may contribute to the severity of symptoms in allergic rhinitis (120) and were suggested to play a disease-modifying role in nasal polyposis, asthma and COPD (121–123) (Fig. 3).

Down-regulation of IgE-mediated inflammation in parasitosis

In Africa, it has been generally found that urbanization is associated with an increased asthma prevalence when compared with rural areas (124–130). Moreover, in rural areas, the prevalence of sensitization to common aero-allergens such as house dust mites is often more common than in urban areas, but skin tests to these allergens are usually but not always negative (131, 132). Some studies suggest that, in tropical areas where parasites are endemic, the relationship between asthma and IgE is different from that of areas without major parasitic disease (131, 133–135).

Many nonexclusive reasons may explain that IgE-mediated hypersensitivity reactions are rare in patients with chronic helminth infections.

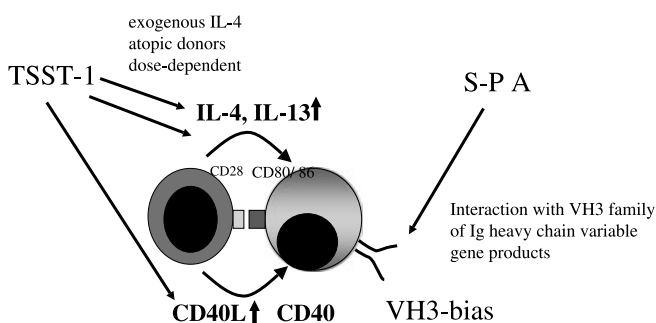


Figure 3. Staphylococcus aureus enterotoxins and B-cell activation: release of cytokines and accessory signals to increase IgE formation.

Differences between asymptomatic subjects and patients with IgE sensitization to allergens

- The inhibition of allergic reactivity in chronic helminth infections is partly due to IgG₄ 'blocking antibodies' in the serum of the infected individual (54, 136–139).
- Th2 responses without atopy may be associated with immunoregulation in chronic helminth infections and reduced allergic disease (140). Elevations of anti-inflammatory cytokines, such as IL-10, that occur during long-term helminth infections have been shown to be inversely correlated with allergy (141, 142). The induction of a robust anti-inflammatory regulatory network by persistent immune challenge offers a unifying explanation for the observed inverse association of many infections with allergic disorders (143).
- Inhalant allergen unresponsiveness of sensitized subjects living in rural areas was associated, at least partly, to a serum factor (R. Van Ree and M. Yazdanbakhsh, personal communication).

Long-term treatment of parasitic patients with anti-parasitic drugs increases the skin test or basophil reactivity to inhalant allergen (70, 144, 145).

Severe anaphylactic reactions because of spontaneous or provoked rupture of the parasitic cyst are well known in echinococcosis (146, 147) and hydatidosis (148, 149).

Treatment of onchocerciasis with diethylcarbamazine may result in anaphylactic reactions (150). Diethylcarbamazine probably acts on the parasite's cuticle, thus exposing it in very large quantities to the body's defence mechanisms. The reaction coincides with the death of microfilariae.

Thus, factors which dampen the IgE-mediated allergic reactions to inhalant allergens are likely to be survival factors for the parasite itself.

Research needs

The hypotheses described above must be prospectively tested to understand the reasons why some sensitized patients are asymptomatic.

Several epidemiologic studies (e.g. ECRHS, ISAAC, birth cohorts) may be used to assess the phenotype of asymptomatic subjects with IgE and subjects with respiratory allergies and IgE. These include the family history, gender, allergens involved (pollens, mites, others), mono- and polysensitization, levels of total and specific IgE or IgG₄. More complex tools such as allergen-specific IgE immunoprints, IgE and IgG_{1–4} against recombinant allergens, IgE affinity and epitopes. In the ECRHS and birth cohorts, the follow-up of patients can be used to investigate the prediction for the development of symptoms in previously asymptomatic subjects.

Birth cohorts can also be used to assess how IgE sensitization leads to symptoms and possibly also who are the subjects who may lose symptoms and IgE sensitization. The risk factors examined in the epidemiologic studies should be tested. In GA²LEN, the inventory of all European birth cohorts is carried out and the data may be used for this research. If blood can be drawn from some of these studies, Treg cells and basophil reactivity may be studied.

Basic mechanisms listed above should be studied in multicentric trial to assess the differences between the two groups of patients first in tree and weed pollen allergy where differences between mono- and polysensitized subjects have already been found. Then, patients allergic to other allergens will be tested. A special insight will be done on mono- and polysensitized subjects. Among the basic mechanisms, Treg cells and the negative regulation of basophils are the most important aspects.

From the basic mechanism studies, novel biomarkers may be found and tested further. Moreover, gene polymorphisms may be tested on samples obtained from existing population studies (e.g. ECRHS).

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