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Reading IgE test results between Science and Culture

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ABSTRACT

IgE is responsible for mediating type I hypersensitivity, causing the degranulation of mast cell or basophil and the fast and show mediators. The reaction is amplified by platelets, neutrophils and eosinophils. IgE has a affinity for its receptor on mast cells and basophils. Subsequently, the exposure to the same allergen, will cross link with the cell-bound IgE and triggers the release of various pharmacologically active substances. More than 80 have been protains have been claimed to cause allergy. The future in this field, will be much brighter if global research is appropriately coordinated and sufficient funds are available to downregulate this antibody. This review seeks to summarize its therapeutic use.

KEYWORDS: IgE, Type I hypersensitivity, Mast cell degranulation, Allergy, Cross-linking, Allergen, Therapeutic downregulation, Immediate hypersensitivity.

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1. INTRODUCTION

There are three main criteria for establishing allergy diagnosis. One must; 1) identify the allergen, 2) establish a causal relationship between exposure to allergen and the occurrence of symptom, and 3) demonstrate an IgE -mediated immunologic reaction (Jensen-Jarolim, Jensen, & Bergmann, 2023; Zhang, Xie, Liu, & Wang, 2022). The allergy history if critical, not only in selecting the appropriate allergens for testing, but also for testing the allergy test results in order to diagnose food allergy, allergic asthma or allergic rhinitis (Ansotegui et al., 2020; Portnoy, 2011). An IgE-related mechanism must be demonstrated, since many exogenous substances may cause otherwise clinically indistinguishable syndromes including bronchospasm and urticaria by mechanisms not related to IgE sensitization of mast cells and basophils (Jimenez-Rodriguez, Garcia-Neuer, Alenazy, & Castells, 2018; Stone, Prussin, & Metcalfe, 2010). The absence of an allergen specific IgE-induced response argues against an allergic mechanism as a cause of the symptoms. To establish the immunologic mechanism, it is necessary to demonstrate the presence of allergen-specific IgE antibodies at a level sufficient to induce an immunologic response following an appropriate antigen challenge in vivo, or by measuring the quantity of allergen specific IgE in vitro (Ansotegui et al., 2020; Kanagaratham, El Ansari, Lewis, & Oettgen, 2020).

Test results for the presence of allergen-specific IgE, whether in vitro (RAST) or in vivo (skin test) may be considered clinically relevant only if there is a history compatible with symptoms induced by exposure to the allergen (Banerji, Solensky, Phillips, & Khan, 2023; Greenhawt et al., 2020; Ocak, Sahiner, Soyer, & Sekerel, 2022). Additionally, test results indicating merely the presence of allergen-specific IgE in the serum do not necessarily indicate that the patient has clinical disease related to exposure to this allergen. All test results must be interpreted in the context of the patient's allergy history, and laboratory tests should not be used as the sole criteria for establishment of the diagnosis of allergy (Ansotegui et al., 2020).

2. LITERATURE REVIW

2.1. HOW RELIABLE ARE POSITIVE ALLERGEN SPECIFIC IGE TEST RESULTS?

A number of studies which have compared in vitro specific IgE tests with skin tests and allergen bronchial challenges have reported good correlations. Generally, the degree of quantitation in the measurement of allergen-specific IgE values is acceptable considering that the allergen extract composition may differ between companies, this correlation being supported by a concordance of approximately 80% between the majority of the in vitro assays . Thus, in vitro allergen specific assays, which make use of well-characterized and in-house standardized allergens with a high level of quality control and quality assurance, provide the most reliable clinical test results. All allergy test results must be interpreted in the context of the test sensitivity (the ability to detect true positive test results), specificity (freedom from false positive results) and efficiency (likelihood of the test detecting only true positives or true negatives) (Abrams & Sicherer, 2016; Anvari, Miller, Yeh, & Davis, 2019).

2.2. TEST SENSITIVITY & SPECIFICITY

Allergen-specific IgE assay sensitivity may vary and depends on the system being used and the quality of the allergens. A number of studies show that sensitivity and specificity are allergen dependent, although allergen-specific IgE directed against the majority of inhalant allergens are generally able to be detected by most systems. Sensitivity ranges from 60% to 95% and specificity ranges from 30%-95%. When discordance is noted this is largely due to differences in the antigens bound on the solid phase matrix of the systems, causing discrepant test results when different systems are employed for the detection of allergen-specific IgE (Antunes, Borrego, Romeira, & Pinto, 2009; Kleine-Tebbe & Jakob, 2015).

2.3. TEST EFFICIENCY

The overall concordance (efficiency) between skin tests and in vitro tests are approximately 70%-90%. Most in vitro allergy tests show a test concordance of 80-90%. It is appropriate to discuss the presence of positive specific serum IgE test results in a clinical, and a laboratory, context separately. Elevated levels of specific IgE may indicate the presence of allergy (Asha'ari, Suhaimi, Yusof, Rushdan, & Che Maraina, 2011; Bignardi et al.,

2019; Rübenhagen & Dangers, 2017). The specific IgE measurement may be useful because it can alert the physician to the possibility of an allergic disease. A strong correlation exists among positive skin tests with common inhalation antigens, high total serum IgE concentration, and the presence of specific IgE against particular antigens (Baldacci, Omenaas, & Oryszczyn, 2001; Khasawneh, Al-Hiary, Al-Abadi, Bani-Salameh, & Al-Momani, 2019; Sinclair & Peters, 2004). However, some patients develop specific IgE against allergens without showing clinical symptoms. The exact mechanism of this is unknown. Although, the presence of specific IgE may also be documented by other laboratory methods (e.g. immunoblotting) and inflammatory cell activation may occur (e.g. histamine release from basophils), patients will not experience symptoms when exposed to the appropriate allergen (Mak & Saunders, 2006).

When patients demonstrate increased levels of specific IgE without clinical symptoms, it indicates sensitization to allergens; however, no clinical symptoms have developed and may never become apparent. An example is beekeeper serum, which may show high levels of specific IgE against insect venoms, however, non-allergic beekeepers never experience allergic reactions when stung by the insects. Low levels of specific IgE to allergens may be perfectly normal as often observed in patients with increased levels of total IgE, e.g. patients with atopic dermatitis. Thus, the positive laboratory result may be correct, however, symptoms are unlikely to appear (Moran & Burks, 2015; Roberts et al., 2016; Scott-Taylor, Axinia, Amin, & Pettengell, 2018).

2.4. WHY MANY POSITIVE RESULTS OCCUR?

Higher serum IgE levels support the diagnosis of allergic disease, but a low IgE does not exclude the presence of an allergic disease. In general, patients with hypersensitivity to several allergens and multiple allergic diseases have elevated serum specific lgE to multiple allergens and those with hypersensitivity to fewer allergens and limited end-organ involvement (e.g. rhinitis) usually have fewer positives (Matricardi, 2023; Xu-De et al., 2021). When interpreting multiple positives, it always necessary to examine the analytical specificity by checking the negative control included in the run. Rarely will patients be positive to all allergens tested. When such patient samples appear, the analytical precision must be checked. In some assays affected by matrix increased serum IgE levels may affect the test results and show binding of specific IgE (Al-Ghonaim et al., 2013).

Typically, the test will show low levels of binding, e.g. class 1 test results. When the test shows all positives at increased levels of IgE, e.g. class 4 results, one should consider repeating the test to check for analytical imprecision. One possible use of the total IgE test is in relation to certain in vitro tests for specific IgE measurements, which are influenced by high levels of total IgE leading to false positive test results. In such situations, a high total IgE test may help the physician to interpret and disregard low class false positives on the specific IgE test. If it is suspected that the test matrix is affected by high levels of total IgE it is not recommended to dilute the serum sample. This way results in diluting out low levels of specific IgE however clinically relevant they may be. It is more appropriate to recommend another test modality, e.g. skin test and to report the in vitro test results as an analytical indeterminate (Ansotegui et al., 2020; Kleine-Tebbe & Jakob, 2015).

2.5. EFFECTS OF ALLERGEN CROSS-REACTIVITY ON IN VITRO TEST RESULTS

The effects of allergen cross-reactivity extend beyond those experienced by the patient. Cross-reactivity may also affect test results. For example, some mite allergens such as tropomyosin, are widely cross-reactive. Periplaneta americana (American cockroach) tropomyosin showed 80%, 81% and 82% sequence identity to tropomyosins from D (Asturias et al., 1999; Jeong et al., 2004; Patel & Meher, 2016; Popescu, 2015). pteronyssinus, D. farinae and shrimp. Likewise, the immunochemical similarity of several of the groups of well-studied homologous grass allergens is extensive. Consequently, when a patient with a grass allergy is tested with a test that has a low specificity for grass allergens, the patient may also test positive to other grasses as well (Duffort, Quintana, Ipsen, Barber, & Polo, 2008; Gangl, Niederberger, & Valenta, 2013).

The same holds true for several free pollens. Several studies have documented clinically important cross-reactivity between pollens from related trees: birch, alder and hazel with certain foods, e.g. apple, nuts. This is a key concern when testing patients in northern parts of Europe, Asia and North America where birch is a common allergen. Assays with lower specificity make it difficult unequivocally to determine the identity of

the symptom-producing allergen. Finally, it has also been observed that certain allergens contain cross-reacting carbohydrate (8). These molecules bind to IgE, however they cannot crosslink IgE molecules. Hence skin test or basophil histamine release will produce negative test results although the in-vitro specific IgE will be positive (Biedermann et al., 2019; Mastrorilli, Cardinale, Giannetti, & Caffarelli, 2019; Vieths, Scheurer, & Ballmer-Weber, 2002).

Unfortunately, one single measurement or observation cannot determine clinical allergy. The specific IgE only constitutes one part of the allergic cascade including inflammatory cells, mediator reliability and end organ sensitivity. This makes the use of serum specific IgE as the sole criteria to determine atopy impossible. Any utilization of a serum specific IgE level must be in the clinical context of the likelihood of the presence of an allergic disease (Ansotegui et al., 2020; Sadreddini & Starkey, 2016; Vieths et al., 2002).

3. DISCUSSION

The interpretation of IgE test results remains a challenging yet essential component of allergy diagnosis. One of the central themes emerging from this review is that a single laboratory measurement—whether specific IgE level or total IgE—cannot independently confirm or exclude clinical allergy. The dissociation between sensitization (presence of specific IgE) and clinical allergy (symptomatic response upon exposure) underscores the complexity of the allergic cascade, which involves not only IgE but also inflammatory cells, mediators, and end-organ sensitivity.

Clinicians must therefore avoid over-reliance on laboratory data alone. A positive specific IgE result without corresponding clinical history may lead to unnecessary avoidance, dietary restrictions, or anxiety. Conversely, a negative result does not rule out non-IgE-mediated or local allergic mechanisms. The concept of "clinical relevance" should guide test ordering and interpretation. This is particularly important in primary care settings where access to allergy specialists may be limited.

Cross-reactivity poses a significant interpretive pitfall. A patient with a true allergy to one allergen (e.g., birch pollen) may test positive to multiple related allergens (e.g., apple, hazelnut) due to homologous protein structures, even in the absence of clinical reactivity to those foods. Advances in component-resolved diagnostics (CRD) have improved our ability to distinguish genuine sensitization from cross-reactive positivity, although these techniques are not yet universally available.

Another critical issue is the variability among commercial immunoassays. Differences in allergen source, extraction methods, solid-phase matrices, and calibration standards contribute to discordant results. Standardization efforts, such as those promoted by the WHO/IUIS Allergen Nomenclature Subcommittee, have improved but not eliminated this problem. Clinicians should be aware of the specific assay used in their laboratory and its known performance characteristics.

From a therapeutic perspective, understanding the limitations of IgE testing is equally important. Biologic agents targeting IgE (e.g., omalizumab) have revolutionized the management of severe allergic asthma and chronic urticaria. However, patient selection for such therapies still requires a comprehensive clinical evaluation rather than reliance on IgE levels alone. Future research should focus on identifying biomarkers that better distinguish symptomatic allergy from asymptomatic sensitization, and on developing globally harmonized standards for allergen-specific IgE testing.

4. CONCLUSION

IgE-mediated hypersensitivity is a complex biological process, and its laboratory assessment requires careful integration of clinical history, physical examination, and test characteristics. Key conclusions of this review are:

1. No single test defines allergy – Both in vitro specific IgE and skin tests must be interpreted in the context of the patient's clinical history.

2. Sensitization ≠ allergy – The presence of specific IgE indicates sensitization, but clinical

symptoms upon exposure are required for a diagnosis of allergy.

3. Test performance varies – Sensitivity, specificity, and efficiency differ across allergens and assay systems, with concordance between skin and in vitro tests ranging from 70–90%.

4. Cross-reactivity is common – Homologous allergens (e.g., tropomyosins, grass pollens, birch-related foods) can cause false-positive or clinically irrelevant results unless component-resolved diagnostics are used.

High total IgE may interfere – Extremely high total IgE can lead to false-positive low-level specific IgE results; alternative testing should be considered.

Clinical judgment remains paramount – Laboratory results are supportive, not substitutive, for expert clinical assessment.

Future progress in the field will depend on international collaboration, standardized allergen panels, improved access to component-resolved diagnostics, and education of both clinicians and patients regarding the appropriate use and limitations of IgE testing. With sufficient funding and coordinated research, downregulation of pathogenic IgE responses and more precise diagnostic algorithms are achievable goals.

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