CAPture highlights three recent articles; the first shows that wheat $\alpha/\beta/\gamma$-gliadins are important markers in wheat-dependent exercise induced anaphylaxis (WDEIA), and the second demonstrates that also in the Mediterranean area storage proteins are the major severity markers in peanut allergy. The last article reviewed describes how sensitization in grass allergy spreads on the component level during childhood.

With the advent of recombinant peanut components the diagnosis of peanut allergy has been improved by allowing the discrimination of patients of different sensitization patterns. That these sensitization phenotypes correlate with different clinical manifestations of the allergy gains more and more support from studies published, which is reviewed in this issue.
Peanut Allergy Focus

For almost 40 years, Thermo Fisher Scientific ImmunoDiagnostics, previously known as Phadia, have maintained global leadership in allergy testing and become one of the world’s leading autoimmune disease test providers. Through clinical excellence, laboratory efficiency and our dedication, we strive to deliver the highest quality and clinical value in our diagnostic tests, as well as providing clinical expertise and scientific information.

This fourth issue of Immunodiagnostics Journal includes a CAPture section with summaries of some recent interesting publications in the field of allergy, followed by an article summarizing the clinical utility of peanut components.

With the introduction of allergen components the diagnosis of peanut allergy has been dramatically improved. Peanut sensitization patterns reveal different phenotypes of peanut allergy that are associated with different clinical manifestations. Not only can component resolved diagnosis help to identify those patients who run a high risk of severe reactions, but they may also contribute to minimizing the need for oral food challenges as suggested in several publications. The review gives references to recent papers supporting the concept of Molecular Allergology in peanut allergy and gives an overview of the peanut components that form the basis for the different sensitization phenotypes. The benefit of combining peanut extract tests and components for an optimal combination of sensitivity and specificity is described based on published results.

I hope that the Immunodiagnostics Journal provides you with an easy way to catch up with or learn more on topics of interest to you.

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**SYNOPSIS**

- Adult patients (age range 17-60 y) with typical history of WDEIA were recruited.
- In five patients co-factors such as aspirin, alcohol and/or infection were involved in eliciting symptoms.
- IgE to wheat extract and to αS-1-gliadin were quantified with commercially available ImmunoCAP® tests using a cut off at 0.35 kU/L. (Phadia Laboratory System, Thermo Fisher Scientific, Uppsala, Sweden).
- Serum IgE to αS-1-gliadin, high-molecular-weight glutenin (HMW-glutenin), alpha-amylase inhibitor dimer (AAI) and wheat LTP were analyzed using experimental ImmunoCAP®.
- The results were basically confirmed in a microarray technology platform.

Citation: Holtmann SC et al. IgE detection to αS-1-gliadin and its clinical relevance in wheat-dependent. Allergy 2012; 67:1457.

**SYNOPSIS**

- Children (n=123) of median age 8 years and with suspected food allergy were recruited.
- Fifty-five children were diagnosed as peanut allergic on the basis of at least two convincing reactions in their clinical history.
- Serum IgE to peanut extract was measured by ImmunoCAP® and to peanut allergen components by ImmunoCAP® ISAC103.
- IgE to peanut extract was higher (p<0.001) in allergic than in tolerant children (median 8.55 kU/L vs. 1.16 kU/L).
- Tree nut allergy was significantly (p<0.003) more common in peanut allergic children.
- No difference in sensitization frequency was shown between peanut allergic and tolerant children with respect to IgE to CCDs, profilin, PR-10 allergens or hazelnut LTP, but not peach LTP were significantly higher in peanut allergic children. (Art 3 v. 3, p<0.025, Cor a 8, p<0.01).3

Sensitization frequencies to mugwort and hazelnut LTP but not peach LTP were significantly higher in peanut allergic children. (Art 3 v. 3, p<0.025, Cor a 8, p<0.01).


**SYNOPSIS**

- Blood samples were collected from a birth cohort (n=820) at 1, 2, 3, 5, 6, 7 and 13 years of age.
- 68% of children sensitized (≥0.35 kU/L) to timothy extract at 3 years of age had developed symptoms before the age 12 years.
- Serum IgE to allergen components (Phl p 1, Phl p 2, Phl p 4, Phl p 5, Phl p 6, Phl p 7, Phl p 11 and Phl p 12) were measured by ImmunoCAP® ISAC technology.
- Both the level of serum IgE to grass extract and the number of components to which children were sensitized increased over time.
- The average number of components to which children were sensitized was 2.1 before symptoms had developed, increased to 3.0 at disease onset and was 3.3 at three or more years after the symptom onset.


**Combined testing of sIgE to αS-1-gliadin and αS-5-gliadin increased the sensitivity to 100% in a population of WDEIA patients**

Serum IgE to αS-5-gliadin has earlier been shown to have an 80% sensitivity to detect wheat-dependent exercise-induced anaphylaxis (WDEIA). The aim of the present study was to analyze the IgE sensitization profiles of adult WDEIA patients (n=17) using well characterized purified wheat allergen components on the ImmunoCAP platform. The diagnosis of WDEIA was based on clinical history and challenge tests of most patients.

Citation: Hofmann SC et al. IgE detection to αS-5-gliadin and αS-1-gliadin, the gap in the in vitro diagnostics of WDEIA might be closed.

**The majority of peanut allergic children in the Mediterranean area are sensitized to storage proteins and not LTP**

Previous studies have shown geographical variations in the sensitization profiles and clinical phenotypes in peanut food allergy. The most established conclusion has been that sensitization to storage proteins dominates worldwide except in the Mediterranean area where sensitization to lipid transfer protein (LTP) related to peach allergy is common.

The aim of the present study was to see if this could be confirmed by comparing sera from unselected peanut allergic Spanish children and peanut tolerant children with suspected food allergy using the ImmunoCAP®ISAC microarray. Sensitization to storage proteins was more common than sensitization to LTP (76% vs. 47%) in Spanish peanut allergic children. IgE to storage proteins was significantly (p<0.001) more common in the peanut allergic than tolerant children (85.2% vs. 14.8%). In contrast, mono-sensitization to LTP was more common in tolerant (79.4% vs. 6%) children. Sensitization to Ara h 2 (72%) was the dominating storage protein sensitization. Test sensitivity increased from 64% to 76% if Ara h 1 and Ara h 3 were also included.

The authors conclude that the majority of peanut allergic children in the Mediterranean area are sensitized to storage proteins like in the rest of the world.

**Oligosensitization to Phi p 1, Phi p 4 and Phi p 5 are early predictive markers for grass pollen allergy**

The sensitization profile of grass allergic patients on the component level has been shown to be very complex. Component-resolved therapy has therefore been proposed in the diagnostic work up preceding the choice of immunotherapy, in order to optimize the treatment by choosing an extract that matches the sensitization profile of the patient.

The aim of the present study was to follow the development of this sensitization complexity to timothy grass pollen in a birth cohort up to 13 years of age. At 3 year of age 6% of the children were sensitized to timothy grass extract but only one of these 38 children reported symptoms. 68% of those sensitized at 3 years developed symptoms later on. The median onset of allergic rhinitis was 7 years of age, with a yearly incidence rate of 2.3% between 3 and 12 years. The average serum IgE levels to timothy extract was 4.0 kU/L in the precipitin phase and increased to 13 kU/L at onset and peaked later on at 24.3 kU/L. IgE to Phi p 1 was the first sensitization to appear in 75% of the infants and was together with Phi p 4 and Phi p 5 the most frequent sensitizations preceding symptoms. Phi p 2 and Phi p 6 sensitizations increased during the onset phase, while Phi p 11 and Phi p 12 (profilin) sensitizations appeared later.

The authors conclude that this increase in sensitization complexity in grass pollen allergic patient might be a reason to start immunotherapy at earlier age in the disease progress.

Clinical Utility of Peanut Components – phenotypic characterization of peanut allergic patients

Background

Peanut allergy is one of the most common food allergies in childhood in many parts of the world, often appearing already during the first two years of life. The prevalence has been estimated to be 1-2%, but this figure varies widely between studies from different countries and also depends on how the diagnosis is made e.g. “reported disease” vs. “challenge verified disease”\(^{(1,2)}\).

Peanut allergic infants often have a concomitant allergy to other foods e.g. egg and milk. Unlike milk and egg allergy, peanut allergy used to be considered a lifelong disease. However, it is now reported that approximately 20% of peanut allergic children develop tolerance within the first five years of life, and that in those with low peanut-specific IgE levels as many as 50-60% may outgrow their peanut allergy\(^{(3,4)}\).

The frequency of peanut allergy appears to have increased during recent years and as allergy to peanut and tree nuts often lead to severe systemic reactions and anaphylactic shock, they have received much attention\(^{(5-9)}\). In the few cases where peanut allergy leads to fatal reactions, mainly adolescents and young adults with concomitant asthma are affected\(^{(10,11)}\).

Peanut allergen components have since several years been used in clinical studies, showing the relation between different sensitization phenotypes and clinical manifestations of peanut allergy. Some of the previous conclusions drawn on prevalence, incidence and tolerance development in peanut allergy based on peanut extract tests may have to be re-evaluated with these new tools.
Sensitization Phenotypes of Peanut Allergy

Recombinant DNA technology allows the efficient production of pure peanut allergen components that today are used for component resolved diagnosis (CRD) in patients with a suspicion of peanut allergy. CRD helps to identify the most serious sensitization phenotypes where the allergic patients run the risk of anaphylactic reactions, and to distinguish these from those who will react only with mild, if any, symptoms. Patients previously diagnosed as peanut allergic may thereby be relieved from daily anxiety as well as unnecessary dietary restrictions.

Peanut allergy related to storage proteins

Peanut allergy associated with sensitization to the storage proteins Ara h 1, Ara h 2 and/or Ara h 3 is the most serious form of peanut allergy, and has now been described all over the world – Europe, USA, Asia and Australia (13-17) – and recently also in the Mediterranean area, where previously peanut allergic children and adults were shown to mainly be of other sensitization phenotypes (18).

The sensitization to storage proteins often appears early in life, even before the age of one year, and can be shown in patients with clinical allergy also to other legumes such as soy (19, 20) and lentils (21) but also to tree nuts (22) and various seeds such as sesame seeds (22-24). Children who suffer from severe atopic dermatitis and who are sensitized to egg and milk during their first year of life appear to be at higher risk of sensitization to peanut and soy storage proteins (15, 25-27).

Peanut allergic patients who develop tolerance over time may be those sensitized to storage proteins, as the disease onset precedes that of sensitization to aeroallergens. Ho et al. showed that low levels (< 3 kU/l) of IgE to peanut extract in the first 2 years or decreasing levels by the age of 3 predict likely remission of peanut allergy (28). A similar decrease in sensitization frequency during the first three years of life has been shown also in soy extract sensitized infants (29). This indicates that sensitization to storage proteins, although associated with severe symptoms, still may be outgrown in early life. Recurrence of peanut allergy has been shown at older age in some studies however if this phenomenon is due to the same storage protein dependent phenotype or is due to an onset of a new, pollen related phenotype, has not been shown (3).

Storage proteins are very stable to heat, low pH and protease activity in the gastrointestinal tract, explaining why this peanut sensitization phenotype is highly associated with allergic anaphylaxis and even death.

Peanut allergen components

<table>
<thead>
<tr>
<th>Component</th>
<th>Protein type</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ara h 1</td>
<td>Storage protein 7S vicilin-like globulin</td>
<td>Peanut specific marker</td>
</tr>
<tr>
<td>Ara h 2</td>
<td>Storage protein 2S albumin, conglutinin</td>
<td>Peanut specific marker</td>
</tr>
<tr>
<td>Ara h 3</td>
<td>Storage protein 11S globulin</td>
<td>Peanut specific marker</td>
</tr>
<tr>
<td>Ara h 5</td>
<td>Profilin</td>
<td>Marker of grass pollen cross-reactivity, low clinical relevance</td>
</tr>
<tr>
<td>Ara h 6</td>
<td>Storage protein 2S albumin, conglutinin</td>
<td>Peanut specific marker</td>
</tr>
<tr>
<td>Ara h 8</td>
<td>PR-10 protein</td>
<td>Marker of tree pollen cross-reactivity</td>
</tr>
<tr>
<td>Ara h 9</td>
<td>nsLTP</td>
<td>Marker of peach cross-reactivity</td>
</tr>
</tbody>
</table>
LTP-related peanut allergy

The LTP (lipid transfer protein) phenotype of peanut allergy, characterized by sensitization to Ara h 9, has mainly been described in the Mediterranean area and is suggested to be caused by cross-reactivity in patients sensitized to peach LTP\(^{17, 30}\). In contrast to storage protein-related peanut allergy, this form of peanut allergy seems to start somewhat later in life, apparently when sensitizations are triggered by inhalant allergens\(^{17}\). Patients with LTP-related peanut allergy are seldom reported to be under 10 years of age and are usually older\(^ {30, 31}\).

LTPs are very stable in the gastrointestinal tracts (low pH, proteases) and therefore LTP sensitization is also a risk factor for serious systemic reactions in peanut allergic patients, although in this phenotype it is also common that only local reactions are elicited.

Although peach allergy is suspected to be the predominant cause of LTP sensitization in the Mediterranean area, up to 25% of the peanut allergic patients are in fact suggested to have primary sensitization to something else than peach\(^ {31}\). Gao et al. recently showed that in Chinese peach allergic patients the primary driver of LTP-sensitization differed depending on the geographical location and exposure to different possible triggers\(^ {32}\), and already previously mugwort and plane tree pollen were suggested to drive LTP sensitization\(^ {32-35}\). In conclusion, there are uncertainties regarding the primary source of LTP sensitization.

Two peanut sensitization phenotypes can give rise to serious systemic reactions; those caused by sensitization to storage proteins and to lipid transfer proteins (LTP), respectively. These are both stable proteins and abundant in peanuts. The profilin and PR-10 phenotypes may be asymptomatic or eliciting mainly local reactions, as these proteins are readily degraded, heat sensitive and of low abundance in peanuts.

Tree pollen-related peanut allergy

Extract based peanut specific IgE tests are often positive in patients living in areas rich in birch due to cross-reactivity between Bet v 1 in birch and its homolog Ara h 8 in peanut. In other geographic areas, PR-10 proteins from other tree pollen such as alder, beech or oak may give rise to the same type of cross-reactivity\(^ {36, 37}\). PR-10 sensitization therefore coincides with the development of inhalation allergies and is mostly seen in children older than 2 years of age.

Food allergic reactions caused by PR-10 sensitization are usually restricted to the oral cavity which can be ascribed to their unstable nature; already in the mouth the allergen is degraded and heated foods are often tolerated.

Thus, the PR-10 dependent sensitization phenotype in peanut allergy is considered a mild form, with low risk for severe reactions. This was nicely and convincingly demonstrated in a clinical study from Sweden where Asarnoj et al. showed that 50% of children sensitized only to Ara h 8 (the level of sensitization to storage proteins Ara h 1, Ara h 2 and Ara h 3 was below 0.35 kU/l) did not react in peanut challenge while 9.7% reacted with OAS at the first two, but not subsequent challenge doses. Only one single individual reported other symptoms (lip swelling, stomach cramping and tiredness), possibly due to sensitization to other storage proteins such as Ara h 6\(^ {38}\).

As always, in assessing the risk of severe reactions to any allergen it is important to be aware of the fact that allergic symptoms are not only based on the allergen specific IgE concentrations but also on the dose of the allergen per se, as well as other contributing factors such exercise, NSAID drugs and infections.

Grass pollen related allergy

Grass sensitization is the most common cause of profilin and cross-reactive carbohydrate determinant (CCDs) sensitization in food allergic patients, and both profilin and CCD antibodies are highly cross-reactive with peanut profilin (Ara h 5) and CCDs\(^ {30}\). It is however broadly accepted that the clinical relevance of these sensitizations is generally low, which is true also in peanut allergy\(^ {30}\).

As for other pollen allergens, sensitization to profilin is mainly detectable after infancy (> 2 years of age). When using recombinant components in the diagnostic testing, sensitization to CCDs is not detected, and thus these clinically irrelevant antibodies do not obscure the test results.
Combining tests for increased performance

Ideally, in vitro diagnostic tests should provide results that enable complete separation of patients in those who have a disease and those who do not, leaving no cases of unclear diagnosis - in other words the positive and negative predictive values should both be 100%. This is however never the case for any allergy test as many different factors influence the clinical symptoms and there is no single measurable marker that alone can discriminate between clinical disease and no disease.

Improved clinical sensitivity

Increased sensitivity of the ImmunoCAP® technology now enables reliable quantification of allergen-specific IgE down to 0.1 kU/l, as compared to previously 0.35 kU/l. As a consequence, the clinical sensitivity has also improved, as shown in recently published studies. In a selected population and using the lower limit of detection (0.1 kU/l), a 100% sensitivity was obtained when diagnosing peanut allergy as compared to 90-96% sensitivity in similar populations when the higher cut off level was applied.

Peanut allergic patients of all phenotypes - storage protein, LTP, PR-10 and profilin - are positive in peanut extract tests when using the 0.1 kU/l cut-off, and thus a negative test excludes peanut allergy with a high degree of certainty, i.e. the NPV is high.

Increasing clinical specificity

A high specificity is needed to obtain a high positive predictive value of a diagnostic test, especially if the prevalence of the disease is low. Increasing the specificity while maintaining the sensitivity improves the test, and in the case of peanut allergy this is now achieved by using CRD in combination with extract based testing. A negative test (below 0.1 kU/l) for the storage protein Ara h 2 excludes storage protein related peanut allergy with a very high probability (although it cannot be fully excluded), and additional testing of IgE antibodies to other storage proteins - Ara h 1, Ara h 3 and Ara h 6 - increases the certainty.

- A negative IgE test (< 0.1 kU/l) to peanut extract likely excludes peanut allergy of any phenotype
- Sensitization to peanut extract but not pollen allergens (tree and/or grass pollen) is a risk profile for more severe peanut allergy (storage proteins, LTP)
- A negative test (< 0.1 kU/l) to Ara h 2 likely excludes “storage protein related peanut allergy”

Of importance for the clinical situation is that predictive values depend not only on the sensitivity and specificity of the test, but also to a high degree on the prevalence of diseased patients in the tested population. As soon as the sensitivity and specificity are less than 100% the positive and negative predictive values decrease rapidly as the prevalence decreases. This means that specific IgE testing never should be used as a screening test in a general population but only be used as an aid for the clinician when there is a suspicion of allergy.
Confirm or exclude peanut allergy

The use of peanut extract based tests

The cut-off of 15kU/l for extract based peanut IgE tests has been widely used in studies and clinical routine to minimize the number of challenges performed[49, 54, 55]. However, this decision point is based on data from a selected population at an allergy specialist level and has low sensitivity since roughly 50% of patients sensitized below this level are clinical reactive[12, 47, 56]. This indicates that test designs solely based on peanut extract can only replace a certain number of food challenges in the clinical routine.

Storage proteins as discriminators

Through many studies it is now well established that sensitization to the storage protein Ara h 2 has the highest potential of the three storage proteins for discriminating between symptomatic and non-symptomatic peanut allergy[12, 47, 53, 57-61]. Decision points of both 100% sensitivity and specificity have been determined in different studies by quantifying IgE to Ara h 2 down to 0.1kU/l[53, 57, 58, 62]. However it must be noted that such decision points also for components are dependent on the kind of patients tested and of the prevalence of the disease in the tested population.

Addition of Ara h 1, Ara h 3 and Ara h 6 specific IgE tests will increase specificity and sensitivity to some degree, as not all patients who develop symptoms show sensitization to Ara h 2[15, 18, 52, 53]. In accordance with this, Ebisawa et al. showed that a combination of all three components increased the specificity but decreased the sensitivity, underlining the dominating role of Ara h 2 for clinical symptoms[15].

Furthermore, it has been shown that both epitope diversity within an allergen component as well as diversity including concomitant sensitization to several different components is associated with a more severe form of storage protein related peanut allergy[63]. This indicates that measuring sensitization to all storage proteins could have additional clinical value for risk assessment[47, 55, 59].

In order to achieve an accurate and safe diagnosis of peanut allergy, it is vital to quantify also very low levels of peanut component specific IgE, as suggested by a study on a population of peanut allergic infants where roughly 20% of those with clinical peanut allergy were shown to have Ara h 2 levels below 0.35 kU/l[52].

It is essential to verify a suspected diagnosis of storage protein related peanut allergy. Equally important, as Sicherer et al. recently pointed out, is to be able to exclude a hidden storage protein dependent allergy in pollen sensitized patients who have mild peanut-associated reactions[64].

- Serum IgE to Ara h 2 is the best discriminator of symptomatic and non-symptomatic sensitization in the storage protein phenotype
- The test combination IgE to peanut extract (high sensitivity) and to Ara h 2 (high specificity) would decrease the need of food challenge test with 50-100%
- IgE testing to additional storage proteins (Ara h 1, Ara h 3, Ara h 6) might lead to improved risk assessment
Reduced need for food challenges

In food allergy, double blind placebo controlled food challenge (DBPCFC) is considered the gold standard for an accurate diagnosis; in practice however open challenges are mostly performed. DBPCFC are cumbersome, expensive and potentially dangerous, and therefore there is a strong need to reduce the number of challenges still reaching a safe and accurate diagnosis. CRD has been shown in several publications to be an aid in fulfilling this need in peanut allergy.

In the study of Codreanu, a cut off of 0.23 kU/l for IgE to Ara h 2 was calculated that distinguished between clinical peanut allergy and non-symptomatic sensitization with a sensitivity and specificity of 93% and 96% respectively, and they concluded that by combining the high sensitivity of the peanut extract based test with the high specificity of the Ara h 2-IgE test, oral challenges could be replaced (52). A similar testing strategy, reducing the need of food challenge was proposed by Lieberman et al. who showed a specificity of 91% using the cut off value 0.35 kU/l (47). A third study that propose an analogous strategy is by Dang et al. where the need of food challenge is shown to decrease by two thirds if infants first are tested with IgE peanut extract and then Ara h 2, and only those with Ara h 2 - specific IgE levels between 0.1 and 1.0 kU/l are selected for challenge test (14). Hong et al. could define an optimal cut off point with a 99.1% sensitivity and 98.3% specificity with only 1.2% misclassification (28), and in a patient population studied by Eller at al. the need of food challenge tests decreased with 55% when using a cut off for Ara h 2 at >1.63 kU/l.

Taken together, these studies suggest that the optimal strategy is to combine extract based peanut IgE tests with quantification of Ara h 2-specific IgE antibodies down to 0.1 kU/l. Application of this diagnostic workup would decrease the need of food challenge test with 50-100% depending on the tested population.

The best guess based on what has been reported up to today is that a decision point with high predictive value (above 95%) for diagnosing storage protein related peanut allergy would be somewhere between 0.25-1.5 kU/l depending on the selected population.

Clinical Utility of peanut CRD

- Helps to exclude clinical peanut allergy
- Helps to confirm clinical peanut allergy
- Identifies patients at high risk for systemic reaction (phenotyping)
- Reduces need for food challenge test in the diagnostic process
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