

CLINICAL ALLERGY IMAGES

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This is one of a series about clinical images relevant to the practice of allergy and immunology. Please submit interesting images and discussion for publication to the Section Editor.

ATOPY PATCH TESTING FOR THE DIAGNOSIS OF FOOD HYPERSENSITIVITY DISORDERS

The spectrum of food hypersensitivity (FHS) disorders has been defined by the WHO.¹ Included in this classification of food-induced immune-mediated reactions are reactions which are either of an IgE or non-IgE immunopathogenesis and which present with symptoms which are of immediate, delayed or mixed onset post exposure.

Tools for the diagnosis of FHS

The diagnosis of an IgE-mediated immune reaction is currently made using one or more of the following diagnostic tools: clinical history, allergy testing (skin-prick test (SPT) and/or specific IgE) and when indicated, oral food challenges. Clinical history and oral food challenges are also relied upon when making a diagnosis of non-IgE-mediated food-induced allergic reactions as existing allergy diagnostic tests perform poorly in this regard. Oral food challenges remain the gold standard for all food-induced allergic reactions. Although an open challenge is usually sufficient for establishing tolerance; a single- or double-blinded challenge is occasionally required for the diagnosis of food-induced allergy, particularly if symptoms experienced under open challenge conditions are equivocal or atypical.

There are however limitations to all the above diagnostic tools. For example, when considering the allergic history, the validity of the diagnosis of food allergy has been shown to be as low as 50% (for all foods)² and as high as 80% for peanut allergy (using defined criteria) (G du Toit – unpublished data). It seems logical that the strength of the clinical history will influence the validity of such a diagnosis. Since 2000, both positive and negative predictive values have been available for the diagnosis (or exclusion) of IgE-mediated food allergy.³ These values were established for children assessed in allergy clinics but may nonetheless be applicable to children in the community (at least for peanut).⁴ Predictive values may also vary with the disease profile of the child, i.e. severe eczema has been shown to be strongly associated with food allergy in childhood. Many children may need to undergo an oral food challenge in order to reach an unequivocal diagnosis of food allergy. Oral food challenges are however only

available to a minority of children as facilities which are able to perform such challenges are generally under-provided and oversubscribed. Additional hurdles to the completion of successful oral challenges include unwilling parents, and young children who may not be compliant or are unable to reach the top challenge dose required. It is also uncommon for food challenges to be performed for the diagnosis of delayed food hypersensitivity, e.g. food-induced eczema exacerbations, despite the not uncommon scenario where young eczematous children return high total and specific IgE results. Dietary elimination of all these positive foods is seldom indicated. This is particularly true for allergens for which predictive values cannot be established, such as soy and wheat. There remains therefore, a need to optimise existing allergen investigations, or alternatively to create novel allergy investigations which may aid in the diagnosis of both immediate and/or delayed food-induced hypersensitivity.

The atopy patch test (APT) and the diagnosis of food hypersensitivity

There are many studies which investigate the use of the APT for the diagnosis of aero-allergen- and contact-allergen-induced allergic reactions. There are also studies which investigate the use of the APT for the diagnosis of immediate and/or delayed-onset food-induced allergic reactions. A position paper which summarises findings to date has recently been published.⁵ Interestingly, these studies appeared in the year 2000 and at around the same time as Hill and Sampson first introduced the concept of cut-off predictive values for the diagnosis of IgE-mediated food allergy. The APT has however not gained widespread popularity outside of allergy research centres. This is due to the fact that the test is technically demanding and time-consuming for staff and patient alike with patients needing to return some 72 hours post APT application for the optimal interpretation of the result.⁶ A renewed interest in the APT has arisen, largely due to the recent marketing (and validation against the Finn Chamber) of a commercial patch testing device (Diallertest).

To understand the potential use of such a device, a brief review of the published APT literature to date is required. The many published studies which assess the performance of the APT (using the Finn Chamber) for the diagnosis of food allergy, seem to share similar statistical findings; namely, high specificities (generally >90%) with low or moderate sensitivities (up to 74%) when compared to the outcome of oral food challenges. Fig. 1 shows an ATP-induced lesion and Figs 2 & 3 demonstrate the Finn Chamber.

Abbreviations

APT	– atopy patch test
FHS	– food hypersensitivity
FPIES	– food protein induced enterocolitis syndrome
IgE	– immunoglobulin-E
MP	– cow's milk protein
SPT	– skin prick test

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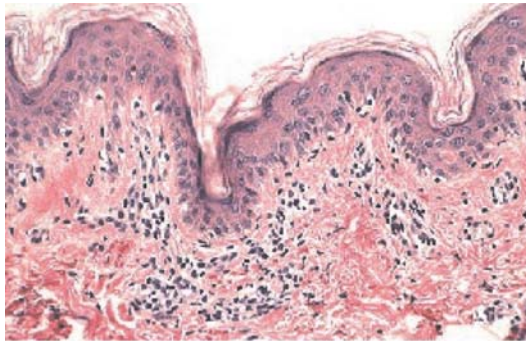


Fig. 1. APT-induced lesion demonstrating an 'eczema-like' late-phase cellular infiltration.



Fig. 2. Finn Chamber preparation.



Fig. 3. Finn Chamber (aluminium) contact dermatitis reactions.

As with SPT and specific-IgE determination, Mehl *et al.*,⁷ demonstrate that the performance of the APT seems to be food-allergen specific, with APTs for cow's milk protein (CMP) and hen's egg performing best. In keeping with SPT and specific-IgE testing, the APT performs poorly for the diagnosis of soy and wheat allergy. The APT performance (as with SPT and IgE testing) seems to improve with the age of the child; however, this is not true for hen's egg allergy where the performance is best between the ages of 1 and 2 years.⁷ Positive APT results seem to predict better for late CMP-induced challenge symptoms and intermediate hen's egg-induced allergy symptoms. The presence of a positive APT may also allow for the application of lower positive predictive levels, thereby allowing for the better selection of patients who are required to undergo oral food challenge tests. An improved APT performance has also been shown if a



Fig. 4. A positive APT result as demonstrated by erythema and more than seven distinct papules.

combination of diagnostic tests is used; in particular, the APT and SPT seem to work particularly well in combination. There is little or no gain (depending on the allergen) when the APT is combined with both the IgE test and SPT. Using all modalities combined demonstrates that at best only 14% of children referred to their specialist allergy clinic could be spared an oral food challenge. Fig. 4 shows a positive APT result.

Community cohorts seem not to share the useful performance characteristics of the APT which were established among children assessed in allergy clinics. A study assessing the performance of the APT in a community cohort (of whom only 20% of children had eczema) could not establish a useful performance of the test when compared to the outcome of oral food challenge. However, only 22 of the 459 children in this community cohort were challenged and mild erythematous reactions were considered as positive.⁸

The APT seems to have a role to play in the investigation of children with non-IgE-mediated gastrointestinal (GI) symptomatology such as the food protein induced enterocolitis syndrome (FPIES) and eosinophilic oesophagitis (EO).^{9,10}

This may prove useful in clinical practice as both of these conditions are frequently accompanied by negative SPT and/or specific IgE test results. In addition, Du Boissieu *et al.*¹¹ published a study which demonstrates impressive statistical performance when using the APT in diagnosing a causative role of delayed CMP – GI symptoms, but in whom CMP SPT results were uniformly negative.

It is true that no single test is sufficiently sensitive and specific for the diagnosis of all FHS disorders. The SPT and/or specific IgE tests, when combined with a detailed clinical history, remain the best diagnostic tests for those reactions which are IgE-mediated. Oral food challenges remain the gold standard for the investigation of scenarios which remain equivocal, despite the use of one or more of the above investigations. In reality however, there are few allergy centres that could cope with the workload generated by this approach, particularly if non-IgE-mediated FHS disorders are included in the challenge burden. It may therefore be that the APT will in time become a more routine investigation, particularly if the advantages and limitations of the test (as suggested by studies to date) are carefully considered.

Standardising the APT

Drawbacks of existing APT techniques include a lack of standardisation of one or more of the following variables: chamber type and size, allergen quantity and quality, vehicle, application adhesive, site of application and interpretation of positive APT sites. The Diallertest

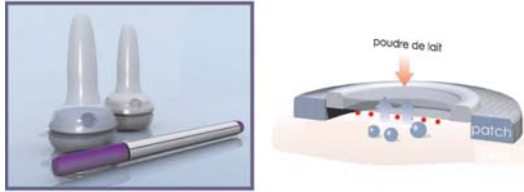


Fig. 5. Diallertest device.



Fig. 6. Diallertest application.

(Figs 5 & 6) is the first commercial attempt at standardising the APT and is soon to be launched in Australia; licence applications have been submitted in Europe. The tests have been validated against the Finn Chamber for CMP, the first allergen to be marketed, but additional food allergens and an aeroallergen (house-dust mite) are to follow. Advantages of the test include ease of application, ability to observe the application site through a transparent membrane and a sustained-release of the allergen onto the skin over the application period. The sensitivity of the Diallertest test appears to be higher than that of the Finn Chamber, and as with previous studies, the specificities remain high.¹²

The anticipated introduction of standardised APT tools such as the Diallertest are to be welcomed as this will allow for greater patient access to the investigation and greater comparison of APT data within and between centres. When reading the results of APTs it remains important that standardised methodologies are followed in respect of the classification of results and time intervals prior to interpretation.¹³ The methodology suggests that it is not sufficient to consider mild erythematous reactions to be positive, particularly if these results are interpreted at home, or by inexperienced practitioners. Exciting possible indications therefore include: the investigation of, and in particular

(given the high specificities) the exclusions of, food-induced eczema exacerbations, non-IgE-mediated food-induced reactions, EE and the FPIES. Although it is easy to generate a test (for any disease) that is either perfectly sensitive or perfectly specific, the test is of little use without some degree of both. Further studies are therefore eagerly awaited in order to adequately assess the true diagnostic value of the APT when assessing children with FHS.

Figure credits

Fig. 4 courtesy of Dr Pete Smith; all other images courtesy of Dr C du Pont.

Declaration of conflict of interest

The author declares no commercial interest in the Diallertest device. An honorarium was however recently received from the marketing company of the Diallertest (Nutritia) for presenting data on the APT in general and Diallertest in particular, while lecturing in Australia.

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