

The role of atopy patch tests in the diagnosis of allergy in atopic dermatitis

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Purpose of review

Recent literature on the atopy patch test, published since 2004, is reviewed to evaluate whether the pathomechanism of the test has become more evident and whether previous studies require standardization.

Recent findings

There is evidence accumulating that a smaller subset of patients with atopic dermatitis show only atopy patch test positivity while specific IgE to the same allergen remains negative. It is possible that local IgE-mediated reactions occur in the skin. New data bring us a step forward in understanding the role of the atopy patch test in diagnosis of allergy in atopic dermatitis but no comprehensive studies were published during the period reviewed.

Summary

Despite recent advances in determining the value and indication for use of the atopy patch test in atopic dermatitis, more objective studies are needed. The atopy patch test may be useful in understanding the mechanisms of atopic allergy, and in defining the clinical relevance of the airborne allergens in eliciting dermatitis. Regarding food allergy, the atopy patch test still requires standardization. To date, methodology differs in all published papers; even the gold standard, the challenge test itself, is not appropriately standardized, which makes the interpretation of results less reliable.

Keywords

airborne allergens, atopic dermatitis, atopy patch test, food allergy

Introduction

The atopy patch test (APT) has received much interest in recent years as a model for studying the pathomechanism of atopic dermatitis and as a complementary test for diagnosing protein allergens causing or maintaining atopic dermatitis either by airborne contact or by food. From the time the name APT was given by Ring *et al.* [1], epicutaneous tests have been performed with allergens known to elicit IgE-mediated immediate reactions with the same allergen. Later, a small sub-group of patients with atopic dermatitis were identified showing a positive APT with no positive circulating specific IgE to the same allergen. The mechanism behind these different reaction types still needs clarification [2]. For diagnostic purposes this group (APT+, skin prick test (SPT)–) is of especial interest in food allergy, for which IgE-mediated reactions have been the only accepted form of evaluating possible allergy.

The methodology of epicutaneous testing with aeroallergens and standardization of test materials have been extensively worked out in recent years by the group of Darsow and Ring [3], but the standardization of APTs with foods needs still much work before it can be recommended for routine clinical diagnostics. The weakness of APT with aeroallergens is the lack of a provocation test: the sensitivities and specificities are calculated by comparison with clinical symptoms. In food allergy the challenge test makes a cornerstone of diagnostics, but as a test it is not completely standardized and therefore the sensitivity and specificity numbers are not always comparable.

Pathomechanism

Holm *et al.* [4•] studied the cellular events in serial biopsies in 10 patients with repeatedly positive APTs with *Dermatophagoides pteronyssinus*. Five of the patients showed specific IgE antibodies to *D. pteronyssinus* in serum whereas five did not. The histological evaluation of the biopsies did not reveal significant differences in dermal cell infiltration scores at different time points in different patient groups although a positive correlation was found between *D. pteronyssinus*-specific IgE in serum and the score of dermal cell infiltrates at 72 h. The biopsies were the same whether the patients were IgE positive or IgE negative. Although the allergen-specific serum IgE amplified the APT reactions, it still remains possible that a local IgE-mediated reaction may occur in

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Abbreviations

APT atopy patch test
HDM house dust mite
SPT skin prick test

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the skin without the presence of elevated specific serum IgE. Another possibility is that there exists a non-IgE-mediated food allergy.

Sensitivity and specificity

There is a great variation in numbers on sensitivity and specificity in the literature on APT. One hundred and six double blind placebo controlled food challenges were performed with egg, milk, soy and wheat in 64 children aged 1–10 years (median 2 years) with atopic dermatitis. The results were analysed retrospectively, comparing total and food-specific IgE; and APTs with native foods. The sensitivities were 76% (food specific IgE) and 70% (APT), respectively and predictive values 64% (specific IgE) and 45% (APT), respectively. Interestingly, APT was positive in five children with positive challenge tests but negative specific IgE to the same food. Thus, a positive APT may be useful in those patients with no specific serum IgE. Twenty-five per cent of all positive challenges were associated with negative food-specific IgE. This high number may be due to patient selection but still suggests that food-specific local T cells may play a predominant role in the pathogenesis of these reactions. The authors conclude that both specific IgE and APT have poor reliability and therefore the double blind placebo controlled food challenges still remain the gold standard in diagnostics for food allergy [5•].

In a multicentre study 314 patients (age range 1.6–80 years) with atopic dermatitis in remission were patch tested with different aeroallergens (*D. pteronyssinus*, cat dander, grass and birch pollen) and food (egg white, wheat flour, celery) allergens. The frequency of clear-cut positive APT reactions ranged from 39% with *D. pteronyssinus* to 9% with celery; and previous eczema flares were reported in 34% after contact with *D. pteronyssinus* and 1% from celery. Clear-cut positive APTs, with all SPTs and specific IgE testing negative, was seen in 7% of the patients, whereas positive APT with negative SPT or specific IgE for the respective allergen were seen in 17% of the patients. APT, SPT and specific IgE results showed significant agreement with the history for grass pollen and egg white. In addition, SPT and specific IgE showed significant agreement with the history for other allergens. With regard to clinical history, the APT had a higher specificity (64–91% depending on the allergen) than SPT (50–85%) or specific IgE (52–85%). No challenge tests were performed [6••].

Previously positive APTs with aeroallergens have been described in persons without atopic dermatitis or in healthy controls. Ingordo *et al.* [7] performed APTs with house dust mite (HDM) extracts (extract of purified bodies of HDM at 20% and with another extract of whole

bodies of HDM at 30%, the latter corresponding to 300 µg/g Der p 1.) in 77 adult patients with atopic dermatitis, 47 atopic patients without eczema and 33 non-atopic participants. Reactions with two different extracts of HDM were positive in 37.7% and 41.6% of patients with atopic dermatitis, 10.6% and 19.1% of atopics without eczema and 12.1% and 12.1% of non-atopic participants. The conclusion is that patients with atopic dermatitis have significantly more positive reactions than non-atopic patients and there is much non-specific reactivity with the APT [7].

Studies on control subjects

The lack of results with APTs in healthy control subjects has been a major problem. Osterballe *et al.* [8•] performed APTs with hen's egg and cow's milk in 486 unselected Danish children at 3 years of age. There was no atopic dermatitis in 381 children who could be regarded as healthy controls. Three hundred and thirty children were studied with APT, SPT, histamine release and specific IgE. Only three were APT+ either for egg or milk and SPT–, whereas 27 children showed specific IgE to egg and two of them were APT+ with egg. Two children had specific IgE to milk, but APTs were negative. In children with negative specific IgE irritant APT reactions were present in 24 of 312 for milk and in 26 of 294 for egg. Oral challenge was performed in 22 children with suspected hypersensitivity to hen's egg or cow's milk. The SPT and histamine release test were shown to have the best diagnostic accuracy. Unfortunately more challenge tests were not performed to control the reliability of the irritant APT reactions. In the study of Darsow *et al.* [6] 10 healthy control subjects remained APT negative.

Reproducibility

Sixteen patients with a history of atopic dermatitis and a history of positive APT reactions were studied as to the reproducibility of APT by Weissenbacher *et al.* The allergen was re-applied at the same time on both forearms and the back. The APT reactions were highly reproducible and positive in 15 of 16 (94%) patients. A reaction was more frequently positive on the back (94%) than the arms (69%) [9•]. Based on those findings it is understandable why Heinemann *et al.* found a low reproducibility rate of their APT results and poor inter-test-agreement with commercial allergens from different suppliers: they first applied the tests on the back and in the follow-up study on the arms [10].

Holm *et al.* [4••] also found a relatively good reproducibility over time: 10/13 patients showed positive results by reapplication of the same allergen. Ingordo *et al.* [7] confirmed a satisfactory repeatability with two different HDM extracts in eight patients with atopic dermatitis, 37 atopic patients without eczema and 19 atopic patients [7].

Test material and method

Breuer *et al.* [5•] used fresh cow's milk and commercial products for hen's egg powder, wheat gluten and soy milk as APT materials. APTs were read at 24 and 48 h after application. Large (12 mm) Finn chambers were used. For a positive APT erythema with infiltration was required. Darsow and Ring used the European Task Force on Atopic Dermatitis guidelines for reading the APTs. Erythema with infiltration was considered positive but stronger reactions required papules in increasing amounts [3]. Contact for 48 h is recommended and the final reading should be made at 72 h, with the antigen applied on a large (12 mm) Finn chambers. The allergens used were well-defined commercial test materials: hen's egg powder (Behr, Hamburg, Germany), wheat gluten (Kröner GmbH, Ibbenbüren, Germany), soy milk (Vitaquell, Hamburg, Germany), and fresh pasteurized cow's milk containing 3.5% fat). Hansen *et al.* [11] also used 12 mm Finn chambers with 48-h application time and final reading at 72 h. Erythema plus infiltration were required for a positive APT reaction. Fresh egg was used as test material. Rancé [12•] used fresh milk and egg, raw peanut powder, wheat powder, soybean milk and mustard powder as patch test materials with large (12 mm) Finn chambers. Osterballe *et al.* [8•] used fresh milk and egg on 8 mm Finn chambers with a contact time of 72 h and read at 72 h. Erythema and infiltration were regarded as positive. In two other studies 8 mm Finn Chambers were used [4,13].

Occlusion time

Rancé [12•] studied the optimal occlusion time for the first time with food allergens (hen's egg, cow's milk, wheat, peanut) in 48 children with atopic dermatitis, aged from 3 to 29 months (median 14 months). Sixty-four open food challenges were performed in the children and the sensitivity and specificity numbers of 24 and 48-h occlusions were correlated to the positive challenge tests. The 48-h occlusion time gave better results than 24-h occlusion: sensitivity was 0.98/0.15, specificity 0.90/0.91, positive predictive value 0.87/0.86 and negative predictive value 0.92/0.63, respectively. The study indicated clearly the use of a 48-h occlusion time [12•].

In another study [6••] with 314 patients with atopic dermatitis, the APTs with both aeroallergens and foods were applied for 48 h; but after 24 h the reactions were read and reapplied with further readings at removal of the tests at 48 h and later at 72 h. Readings of APT at 24 h gave very few reactions in comparison with 48–72 h readings, which are recommended.

Vehicle and tape stripping

Oldhoff *et al.* [13] compared APTs with allergens dissolved in aqueous solution on tape-stripped skin with

petrolatum without tape stripping. Nine out of 13 patients showed positive reactions to allergen in both vehicles but reactions were significantly stronger with petrolatum. No differences were found histologically in numbers of eosinophils, T-cells or neutrophils in the different groups and the authors consider both methods feasible for APT [13].

Control materials in atopy patch testing

Different materials have been used as controls in the APT without any simultaneous comparison between them. Darsow *et al.* [6] used the vehicle, petrolatum, as a negative control. Positive reactions to the vehicle were seen in three of 302 patients (0.99%). One of 10 patients showed a positive APT reaction to the negative control physiological saline [11]. Holm *et al.* [4••] left the control material (petrolatum) for 72 h under occlusion before biopsy. The tests were clinically negative but in three control patches there was a slight cellular infiltration in patients with elevated amounts of specific IgE to *D. pteronyssinus* in serum. Often a control material is not used or not mentioned [5,8•,9•, 12•].

Adverse effects of atopy patch testing

In the 314 patients of Darsow *et al.* [6••] adverse effects were recorded in 7.7%. They were mostly mild like local flares, contact urticaria, irritation from adhesive tapes and local itching. One subject experienced breathing problems on the night following APT and SPT. The patient recovered with removal of the APT and showed a negative chest radiograph. A causal relationship to the APT was considered unlikely.

Provocation tests

There is no provocation test protocol to confirm the relevance of airborne allergens as a cause of atopic dermatitis and therefore all results regarding sensitivity and specificity are based on objective clinical symptoms. Food allergy was confirmed by challenging the patient with the offending food. Unfortunately, food challenge protocols have not been standardized. Recently, a European position paper has been published on immediate reactions to foods but none for delayed type reactions [14]. Since APT has been developed to diagnose and understand the pathomechanism of dermatitis caused by a specific allergen, challenge tests should be evaluated after several days.

In the papers referred to here several modes of challenge procedure are described. Breuer *et al.* [5•] administered an allergen at increasing amounts on the first day and followed the reactions over 48 h. The reactions were called immediate when taking place within 6 h of the last dose. They performed double blind placebo controlled

food challenges and soy formula was used as a negative control [5•].

Rancé [12•] used the open food provocation test, on children 3–29 months of age. Osterballe *et al.* [8•] performed oral challenges in children with possible food hypersensitivity to cow's milk or hen's egg. Possible food hypersensitivity was defined as self-reported hypersensitivity (questionnaire) or a positive outcome in at least one of the test procedures (SPT/APT) without a clear-cut negative case history.

Conclusion

From the studies discussed, it can be concluded that a 48-h occlusion time is most reliable, the back is better than the forearm for applying the APT, and the APT seems to be fairly reproducible. Unfortunately more important questions still remain unanswered. Lack of a challenge test makes the value of the APT with aeroallergens questionable, but these tests in adults can be used for studying the mechanism of atopic dermatitis because biopsies from adults are ethically easier procedures than in children. Once there is some conformity with performing challenge tests with foods, both for immediate and delayed type reactions, the specificity, sensitivity and both positive and negative predictive values of APT can be calculated correctly. Standardization of test materials and methods still needs well-planned multicentre studies.

Probably the most important use for APT will be diagnosing relevant food allergens in multi-allergic children (under the age of 2 years preferably) with a negative SPT and no food-specific IgE in serum. It is relatively easy to diagnose milk and egg allergies with challenge tests, but if atopic dermatitis continues or gastrointestinal symptoms complicate the situation, APTs may suggest which foods should be suspected and possibly eliminated from the diet. Multiple challenge tests can be clinically difficult for the patient and family. APT with pollens and animal dander deserve further evaluation, especially, in children with exacerbations of their dermatitis during the pollen season or those in contact with animals, with negative SPTs or in-vitro IgE tests.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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