

Atopy Patch Testing

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KEY CONCEPTS

- In addition to specific serum IgE and skin prick test (SPT), atopy patch testing (APT) may be helpful in unclear and discrepant diagnostic situations.
- In selected cases, the combination of APT and specific IgE or SPT may make double-blind, placebo-controlled food challenges superfluous for suspected cow's milk and hen's egg allergy.
- Since an oral food challenge rarely becomes superfluous, the APT plays no role in the daily routine use, but should be further investigated in controlled studies.
- The ultimate test for suspected food allergy is still a correctly performed controlled oral food challenge.

Introduction

The atopy patch test (APT) is performed epicutaneously, but instead of using typical type IV allergens (such as metals or perfumes), typical immediate type I allergens (aeroallergens or foods) are used. Due to the fact that other diagnostic tests cannot predict clinically relevant food allergy precisely enough, increasing attention has been paid to the APT lasting recent years. Recently, a consensus paper was published [1].

History

APT was first reported in the literature in 1982 using aeroallergens [2]. A Finnish group later reported on a possible role for the APT in food allergy [3]. The authors proposed that the skin prick test (SPT) and specific IgE in serum might reflect early clinical reactions to the offending food (clinical symptoms within 2 hours), while the APT might have a high predictive capacity for late-phase clinical reactions during double-blind, placebo-controlled food challenges (DBPCFCs) [3–5].

Pathogenic mechanisms

The pathogenic mechanism involved in the APT has not yet been studied in detail. The close macroscopic and microscopic similarities between the specimens from APT sites

and lesional skin of patients with atopic eczema (AE) indicate that the APT may be a valid model to study allergic inflammation in AE [6]. In particular in food-sensitive AE, T-cells obviously play an important role as shown in recent studies [7,8]. In line with the previous findings, our earlier clinical investigations indicate that positive APTs (with T-cell infiltration of the skin) correlate with clinical late-phase responses [9].

Additional evidence is provided by a study showing that APT reactions are associated with T-lymphocyte-mediated allergen-specific immune responses [10]. A recent investigation has demonstrated that the chemokine pattern (CXCR3 activating chemokines) in skin biopsies can be used to distinguish between allergic and irritant patch test reactions [11]. Other authors have shown that a biphasic cytokine expression is typical for house dust mite allergen patch test reactions but not for irritant reactions [12].

Performance

The APT should be performed on uninvolved skin – usually on the patient's back [9]. Twelve-millimeter aluminum cups (e.g. Finn Chambers on Scanpor) should be used to cover filter paper on which one drop (50 µl) of the foodstuff preparation has been applied [13]. Native foods are preferred, for example, fresh cow's milk (CM), native hen's egg (HE), wheat-powder dissolved in water, and soy milk. For aeroallergens, commercially available extracts may be used; in most studies petrolatum is used as a vehicle. While the use of a negative control, for example saline, is recommended, a positive control does not seem necessary.

The cups are removed at the end of the 48-hour occlusion period, and 24 hours later reactions are classified as positive or negative (Table 22.1). Unfortunately, the reading of the APT is highly dependent on the experience of the evaluator. One study proposes a standardized interpretation of the APT after having investigated the sensitivity, specificity, and predictive values for each skin sign in relation to the oral food challenge outcome [14]. The authors classify the APT reaction as positive if there is erythema plus clear infiltration/papules [14]. A further important criterion is the so-called “crescendo” or “decrecendo” reaction: while an allergic site shows a “crescendo” of erythema and infiltration, that is increasing erythema and infiltration at the test site, a skin irritation response characteristically tends to clear between 48 and 72 hours. The reading of the APT should result in a clear yes or no answer. A grading system does not seem to be helpful in daily decisions. Figure 22.1 shows a positive APT.

A few studies have investigated the possible modulation of the APT by an anti-inflammatory skin treatment: both glucocorticosteroids and tar reduce the macroscopic outcome of the APT reaction and the influx of inflammatory cells [15]. A similar effect could be shown for the topical immunomodulator pimecrolimus [16]. The practical

consequence is that the APT should be performed on skin with no previous local treatment. No information is available concerning the implications of treatment with oral antihistamines, although no influence would be expected on the basis of the pathogenic mechanisms of the T-cell-mediated late-phase reaction of the APT, but erythema may be decreased. Therefore, antihistamines should be withdrawn at least 48 hours prior to the APT.

The application sites should be checked after 15 minutes for immediate local reactions. Especially with egg, contact urticaria may occur and uncomfortable pruritus may make it necessary to stop the APT. Apart from local urticaria (Fig. 22.2), side effects are rare; systemic side effects have not been reported.

Indications

The APT with food may be performed in any case of food-related symptoms – especially if (1) AE is the underlying disease, (2) late-phase clinical reactions are expected, or

Table 22.1 Assessment of the APT

Allergic	Irritative
Jagged margin	Sharp margin
Marked erythema	No or mild erythema
Papules, infiltration	Bulla, necrosis
Crescendo phenomenon	Decrecendo phenomenon
Persistent reaction	Short duration

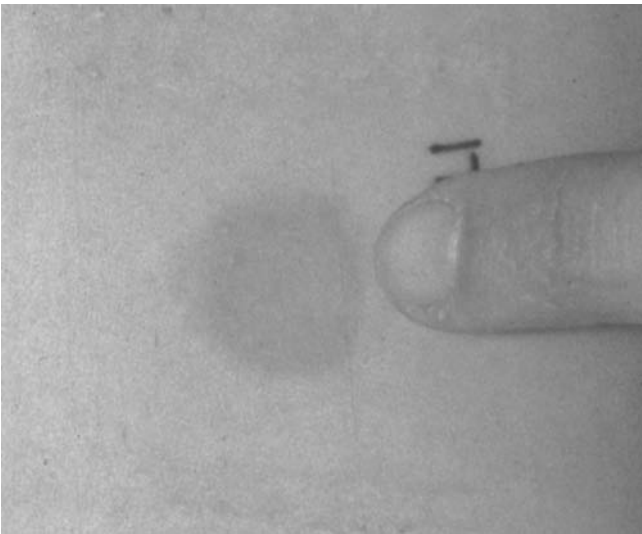


Figure 22.1 Positive APT.



Figure 22.2 Local urticaria as a possible side effect of APT.

(3) specific serum IgE or SPT is negative. An APT with aeroallergens may be indicated if pollen or house dust mites are suspected to exacerbate the underlying eczema.

Clinical studies

Atopic eczema

One study investigated 75 children (median age 2.1 years) with AE and suspected food allergy by DBPCFC, specific IgE in serum, SPT, and APT [9]. In 66 of 77 (86%) positive oral challenges, specific IgE in serum to the corresponding allergen was positive, in 64 of 77 (83%) the SPT, and in 42 of 77 (55%) the APT was positive. Immediate type clinical reactions were associated with positive SPT and proof of specific IgE in serum. While the sensitivity of late-phase clinical reactions was 76% and specificity was 95% for the APT, corresponding figures for the SPT were 58% and 70%, and for the specific IgE in serum 71% and 29%, respectively [9]. Other studies investigating the APT with cow's milk [17,18], wheat [19], and peanut [20] reported similar findings.

A further study investigated whether the combination of the APT, SPT, and specific IgE in serum could improve the diagnostic value [21]. The APT was again the best single predictive test (PPV 95%) for evaluating suspected CM allergy, and the combination of a positive APT with evidence of specific IgE, or APT together with a positive SPT optimized the PPV to 100%. For HE allergy, the APT was also the best single predictive test (PPV 94%); in this case the combination of two or more tests was no better in terms of predictive value than the APT alone. In both CM and HE challenges, the predictability of oral challenges depended on the level of specific IgE in serum. For wheat allergy, the APT proved to be the most reliable test and the PPV of 94% could not be improved by a combination with other allergy tests. The authors concluded that the combination of a positive APT together with defined levels of specific IgE (CM > 0.35 kU/l and HE > 17.5 kU/l) might make DBPCFC superfluous for suspected CM and HE allergy [21]. Other authors also found that the combination of APT with SPT improves the diagnostic value of the APT [22]. A further study showed that the combination of a negative APT and SPT could exclude CM allergy in children who have allergic manifestations other than atopic dermatitis [23].

Very recent data obtained from a large number of children ($n = 437$) who underwent 873 oral food challenges, and in which 1700 single APT were performed, indicated that although the predictive capacity of the APT is improved when combined with the specific serum IgE or SPT, an oral food challenge only becomes superfluous in a few children [24]. In addition, the APT is time consuming and demands a highly experienced evaluator. For daily clinical practice, the APT does not seem to add enough information to justify its routine inclusion in the diagnostic work-up of suspected food-related symptoms [24].

Gastrointestinal diseases

The APT has only marginally been studied in gastrointestinal food-allergic diseases. In one study, 26 children (mean age 6.9 years) with biopsy-proven eosinophilic esophagitis (EE) were investigated by SPT and APT and a 6-week elimination diet was initiated on the basis of these results. Eight of the 26 children showed full resolution of symptoms and 6 of 26 partial resolution [25]. The authors concluded that the combination of SPT and APT could identify potential causative foods that might contribute to the pathogenesis of EE [25]. The same group reported in a follow-up study in 146 patients with biopsy-proven EE that symptoms improved after elimination diets directed by APT and SPT with CM, HE, and soy [26].

Another study investigated 35 children with non-specific, solely digestive symptoms – without an underlying AE [27]. In these patients, aged 2–57 months, 24/35 children were considered to be CM allergic due to mostly open oral food challenges. Of these 24 children, 19 showed a positive APT, while only 3 had a positive SPT [27]. The authors recommend using the APT in patients with CM allergy and digestive symptoms. The most recent study investigated a small number of infants and young children ($n = 19$) with food protein-induced enterocolitis syndrome (FPIES) and found that APT predicted the result of the oral food challenge in 28/33 cases [28]. All 12 patients with a negative APT had a negative oral challenge to the suspected food. The authors stated that the APT appears to be a promising diagnostic tool for the diagnosis of FPIES [28].

Aeroallergens

Several studies have investigated the role of the APT for aeroallergens, mostly for house dust mites, for example a European multicenter study [29]. However, the problem of the APT with aeroallergens is that no gold standard exists with which to compare the results. In contrast to food, where controlled oral challenges can be used, the clinical relevance of the role of house dust mites in AE, for example, cannot be assessed in any standardized fashion.

Open questions

Despite some advances in the efforts to standardize the APT [1], there are still several open questions [13]. While it could be shown that 12-mm cups are superior to 6-mm cups [30], that the occlusion time of 48 hours is preferable to 24 hours [31], and that age (within childhood) does not seem to play an important role [32], it is not clear whether the APT works only in children with AE or also in other clinical conditions. Unpublished data point to a considerably higher sensitivity in children with atopic dermatitis compared to those without. Furthermore, it is not known whether the APT is able to predict the development of

tolerance after a period of elimination of the corresponding food. Finally, it is completely unclear whether the APT itself can lead to sensitization of children who would not otherwise be sensitized.

The atopy patch testing in the daily practice

In conclusion, the current role of the APT in the daily diagnostic work-up of suspected food-related symptoms can be characterized by the following statements [33,24]:

- 1 In addition to specific serum IgE, SPT, and history, the APT may be helpful in unclear and discrepant situations.
- 2 The APT plays a role in assessing clinical late-phase reactions during oral provocations.
- 3 In selected cases, the combination of a positive APT together with defined levels of specific IgE or SPT may make DBPCFC superfluous for suspected CM or HE allergy.
- 4 However, the APT is time consuming and demands a highly experienced evaluator.
- 5 Since an oral food challenge only becomes superfluous in a few children even when the APT is combined with serum IgE and SPT, the APT has no role in the daily routine use, but should be further investigated in controlled studies.
- 6 The ultimate test for suspected food allergy is still a correctly performed controlled oral food challenge.

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