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ORIGINAL PAPER

Allergic skin disease: investigation of both immediate- and delayed-type hypersensitivity is essential

N. Usmani and S. M. Wilkinson
Dermatology Department, Leeds Teaching Hospitals, Great George Street, Leeds, UK

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Summary

Background In our clinic we routinely patch test patients referred from occupational health for the investigation of latex contact urticaria. We also undertake both patch and prick testing (where indicated) in patients referred with persistent dermatitis/eczema. If investigation of allergic skin disease is undertaken by a non-dermatologist, it is unlikely that patch testing will be performed.

Objective To carry out a retrospective analysis of patients who had been prick tested to establish whether an incomplete diagnosis would have been reached if patch testing had been omitted.

Methods Details of patients who had attended for patch testing between July 2004 and December 2005 were analysed. Patients who had had prick tests and patch testing were identified. The outcomes of prick tests and patch testing were documented together with the clinical relevance.

Results Three hundred and thirty out of 1060 patients referred to the clinic were prick tested. 54.2% patients were referred from dermatologists. 26.6% were referred from occupational health, 68 patients had positive reactions on prick testing of whom 36 had positive patch tests (52.9%), which were of current relevance in 27 patients (39.7%). Nine out of 106 health workers referred to exclude latex contact urticaria had positive prick tests to latex. Fifty of these patients demonstrated delayed-type hypersensitivity with nickel, cobalt, rubber and its additives being the most common allergens found. Of the 262 patients who had negative prick tests, 121 had positive patch tests (46.1%) of current relevance to patient history in 92 subjects (35.1%). While none of the six patients referred for investigation of reaction to local anaesthetics had a positive prick test, one was allergic to local anaesthetic on patch testing.

Conclusion Omission of patch testing from the investigation of allergic skin disease, even when contact urticaria may be the sole suspected diagnosis, would result in the frequent missed diagnosis of contact allergy. We recommend that patients with suspected allergic skin disease are investigated in an environment where investigation of both immediate- and delayed-type hypersensitivity can be undertaken. In particular, patients with atopic eczema, suspected latex rubber allergy, hand dermatitis (particularly occupational) and drug reactions should be targeted to receive both investigations.

Correspondence:
N. Usmani, Dermatology Department, Leeds Teaching Hospitals, Great George Street, Leeds, LS1 3EX, UK.
E-mail: nailausmani@hotmail.com

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Introduction

Although patch testing is the gold standard for diagnosis in allergic contact dermatitis, prick testing is an important tool for ascertaining IgE-related immediate-type hypersensitivity. The British Association of Dermatology guidelines for the care of contact dermatitis emphasize the importance of such testing in occupations at risk of protein contact dermatitis such as chefs and veterinarians. It is also particularly important in health workers with hand dermatitis where immediate-type hypersensitivity to

natural rubber latex (NRL) may complicate allergic, irritant or atopic hand dermatitis. In such clinical situations, the guidelines suggest that positive results from prick testing are likely to be seen in combination with delayed-type hypersensitivity to NRL or rubber additives on patch testing [1].

Prick testing is currently undertaken by dermatologists, allergists and immunologists, chest physicians and ENT departments. If carried out by a non-dermatologist, it is unlikely that patch testing will be performed.

In our clinic, we routinely patch test patients referred from occupational health for the investigation of latex contact urticaria and in those referred with suspected immediate-type reactions to drugs. We also undertake both patch and prick tests (where indicated) in patients referred with persistent dermatitis. Our aim was to carry out a retrospective analysis of patients who had been prick tested to see how many of these patients had relevant positive patch tests.

Materials and methods

Details of patients who had attended for patch testing between July 2004 and December 2005 were retrieved from a comprehensive database providing clinical details of all patients attending the contact dermatitis clinic at the Leeds General Infirmary. The majority of patients were referred for the exclusion of suspected allergic contact dermatitis with prick testing performed where clinically indicated. Individuals referred with a suspected drug reaction or latex contact urticaria had both patch and prick testing. An analysis of those patients who had both prick and patch testing was then performed. Data including age, sex, occupation, duration of condition and source of referral were recorded. Atopic status, sites affected and whether the condition was work related were also noted. The outcomes of prick tests and patch tests as well as allergens to which the patients had been tested against were documented together with clinical relevance.

Results

Data from 1060 patients who had attended clinic were reviewed. Of these patients, 330 patients had had prick tests performed and data from this subset of patients were analysed further. Demographics and some basic clinical data of this population are shown in Table 1. In general, children tended to present with a generalized distribution of eczema whereas patients referred for work-related conditions suffered mainly from hand dermatitis.

All patients who attended for prick testing were also patch tested to the British standard series along with other series dependant on history. Table 2 summarizes the relevant positive reactions on both prick and patch testing.

Table 1. Demographic details of the population

Patient group	$N = 330$
Sex	
Male	79
Mean age	36.6 years (range 4–85)
Atopy	
Y	195
Duration of condition	
0–3 months	20
4–12 months	116
1–3 years	70
3–7 years	51
8 years	69
Unknown	4
Sites affected	
Leg	14
Face	36
Arm	5
Hand	127
Occupation related	
Y	200

Y, yes.

A total of 179 patients (54.2%) were referred from dermatologists within or outside of the hospital, of whom 87 had positive patch tests relevant in 79 patients (current relevance in 66). Eighty-six (26.6%) were from the occupational health department and 39 of them had positive patch test results, relevant in 30 patients (current relevance 15). The remaining 65 patients were referred from general practice, with 31 positive on patch testing relevant in 28 patients (current relevance 22).

Sixty-eight patients had positive reactions on prick testing, of whom 36 had positive patch tests (52.9%), which were relevant in 32 patients (47.1% – current relevance 39.7%). Nine out of 106 health workers referred to exclude latex contact urticaria had positive prick tests to latex. Fifty of these patients demonstrated delayed-type hypersensitivity, with nickel, cobalt, rubber and its additives being the most common allergens found.

Of the 262 patients who had negative prick tests, 121 had positive patch tests (46.1%), relevant to patient history in 108 subjects (41.2% – current relevance 35.1%).

Discussion

Prick testing remains a pivotal test within an increasingly allergic population. It is minimally invasive and when performed correctly has good reproducibility [2]. In current practice, it is performed by allergists, immunologists and dermatologists as well as by other clinical specialties such as ENT surgeons and chest physicians. In our series, the main indications for prick testing were the exclusion of contact urticaria in individuals with hand dermatitis,

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Table 2. Summary of results of patch and prick testing in different patient groups

Indication	Allergens tested on prick testing	Patients prick test positive	Patients prick test negative	Positive allergens on prick testing	Patients patch test negative	Patients patch test positive	Positive allergens on patch testing
Health care workers (n = 106)	Latex	9	97	Latex (9)	56	50	Nickel (15 pr 4 cr 1 nr), colophonium (1 cr 3 pr), parabens (2 cr), formaldehyde/releasers (6 cr), fragrance mix 1 (4 cr 1 pr), thiuram (2r), mercaptobenzothiazole (1r), carba mix (1r), mercapto mix (1r), PPD (4 nr 2 pr), Balsalm of Peru (2 pr), cobalt (8 pr 1 cr), tixocortal (1 cr), MeCl (3 cr), propolis (2 cr 1 pr) *Hairdressing series*: *p*-toluenediamine sulphate 1 pr *Face series*: thiomersal (2 cr 1 pr 9 nr) *Rubber series*: *N*-cyclohexylbenzothiazyl sulphenamide (2 cr), dibenzothiazyl disulphide (2 cr), morpholinyl mercaptobenzothiazole (1 cr), 1,3 diphenylguanidine (1 cr), tetramethylthiuram monosulphide (1 cr), tetramethylthiuram disulphide (1 cr), tetraethylthiuram disulphide (1 cr), dipentamethylenethiuram disulphide (1 cr), PVC glove (1 cr) *Dental series*: mercury (1 cr), diurethane dimethylacrylate (1 cr) *Photopatch series*: homosolate (1 cr) *Plant series*: tea tree oil (1 cr), gold (1 cr)
Cleaners, hairdressers (n = 19)	Latex	2	17	Latex (2)	8	11	Nickel (5 pr 1ur 2 nr), colophonium (1 cr), lanolin (1 cr), fragrance mix 1 (1 pr 1 cr), PPD (2 cr 1 pr), cobalt (3 pr) *Hairdressing series*: *o*-nitro-*p*-phenylenediamine (2 cr), *p*-toluenediamine sulphate (3 cr), glyceryl monothioglycolate (2 cr), ammonium persulphate (4 cr), 4 amino-phenol (2 cr), cocamideopropyl betaine (1 cr) *Plant series*: lichen acid mix (1 cr) *Face series*: cocamide DEA (1 cr), glycerol monothioglycolate (1 cr)
Chefs, housewives (n = 19)	Latex foods	6	13	Latex (4), tomato (1), egg (1), cod (1)	12	**7**	Nickel (2 pr 2 cr 1ur), fragrance mix 1 (1 cr), carba mix (1 cr), thiuram (2 cr), mercaptobenzothiazole (1 cr), PPD (1 cr), cobalt (1 cr), primin (1 nr), tixocortal (1 cr) *Fingertip series*: tosylamide/formaldehyde resin (1 cr), diallyldisulfide (1 cr) *Face series*: thiomersal (1 cr) *Bakery series*: propyl gallate (1 cr) *Rubber series*: *N*-cyclohexylbenzothiazyl sulphenamide (1 cr), morpholinyl mercaptobenzothiazole (1 cr), tetramethylthiuram monosulphide (1 cr), tetraethylthiuram disulphide (2 cr), dipentamethylenethiuram disulphide (1 cr), rubber glove (1 cr) *Metal series*: palladium chloride (1 cr)

Table 2. Continued

Indication	Allergens tested on prick testing	Patients prick test positive	Patients prick test negative	Positive allergens on prick testing	Patients patch test negative	Patients patch test positive	Positive allergens on patch testing
Adults with atopic dermatitis ($n = 78$)	Airborne allergens foods	29	49	HDM (4), tree (1), grass (3), horse (1), dog (7), egg (1), cod (4), barley (2), milk (1), yeast (1), tomato (2), cherries (2), pear (1), apple (2), peach (1), kiwi (1), onion (1), potato (2), peanut (2), hazelnut (1), almond (1), flour (1), marshmallow (1)	34	44	Nickel (12 pr 4 cr 1 nr), colophonium (2 pr 1 cr), cobalt (4 nr 7 pr), parabens (1 cr), formaldehyde releasers (1 cr), wool alcohols (1 nr 1 cr), MeCl (1 cr 1 pr), epoxy (1 cr), fragrance mix 1 (8 cr 1 nr), chlorocresol (1 cr), thiuram (4 cr), carba mix (2 cr), PPD (2 pr 1 cr 1 nr), balsalm of peru (1 cr 1 nr), PCMX (2 cr), methyldibromoglutarilenitrile (1 pr), primin (1 cr), sesquiterpone (3 cr), tixocortal (4 cr), polyfax (1 cr), lyral (1 pr) *Face series*: amerchol (1 cr), methylene-bis-oxazalidine (1 cr), thiomersal (1 cr 1 pr), propolis (1 cr), lanolin (2 nr), dimethylaminopropylamine (1 nr), thiomersal (1 nr) *Plant series*: *T. officinale* (2 cr), *C. romana* (1 cr), lichen acid mix 1 (ur) *Rubber series*: *N*-cyclohexylbenzothiazyl sulphenamide (1 cr), dibenzothiazole disulphide (2 cr), dipentamethylenethiuram disulphide (1 cr), 1,3 diphenylguanidine (2 cr), tetramethylthiuram monosulphide (1 cr), tetraethylthiuram disulphide (1 cr), hexamethylenetetramine (1 cr), PVC glove (1 cr 1 pr)
Children with atopic dermatitis (< 16) ($n = 9$)	Airborne allergens foods	7	2	HDM (3), grass (2), dog (1), cat (1), apple (1), grape (1), orange (1), banana (1), tomato (1), amylase (1), peanut (1), kidney bean (1)	4	5	IPPD (1 nr), nickel (1 pr), potassium dichromate (1 nr), fragrance mix 1 (1 cr), cobalt (1 pr) *Medicament series*: thiomersal (1 cr)
Reactions to drugs ($n = 6$)	Lignocaine, prilocaine	0	6		4	2	Nickel (1 pr), fragrance mix 1 (1 pr), cobalt (1 pr), photo patch series (1 cr), latex (1 cr), caine mix (1 pr), rubber additives (3 cr)

cr, current relevance; pr, past relevance; nr, not relevant; ur, unknown relevance.

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investigation of individuals with atopic dermatitis (AD) and of suspected drug reactions.

Although patch testing is confined to dermatology practice in the United Kingdom, Farrell et al. [3] showed that 53% of allergists in the United States also performed patch testing. The majority however patch tested five or fewer patients per month with 33% performing only a single patch test reading. The accuracy of results obtained in this way must be questioned, as single patch test readings will inevitably result in false-negative reactions and this was confirmed in a study of 4721 patients who were patch tested in whom 24% of all allergic reactions were negative on day 2 [4]. Diagnosing and interpreting patch test results correctly is a skill that comes with experience and the importance of formalized training in patch test reading and interpretation cannot be disregarded [5]. This was demonstrated in a study of 100 patients referred for patch testing in whom a comparison was made between patch tests read and interpreted by a consultant dermatologist with an interest in contact allergic dermatitis and by an experienced registrar who had not yet received any formalized specialized training. Results showed a variation in patch test reading and interpretation between the consultant and registrar in 10% of patients. Patch testing using allergens from series in addition to the European standard revealed further relevant contact allergies in 19 patients. In 14 patients, allergies would have been missed by limited additional series. This study confirmed the value not only of specialist training but also of a specialist clinic in the diagnosis of contact allergy with knowledge and availability of a wide range of allergens [6].

The results of our study show that a significant proportion of patients referred for investigation for prick testing had positive results on patch testing many of relevance to patient history (47.5% with relevance in 41.5%). Of those patients referred by occupational health, virtually all of whom were referred to exclude latex contact urticaria, a significant proportion had positive patch tests (45.3%) with current relevance in 17.4%, emphasizing the importance of dual testing in such individuals. In a study, which looked at IgE- and cell-mediated hypersensitivities in a Danish population, serum IgE, prick tests and patch tests to environmental haptens were performed in 561 patients [7]. One or more positive prick tests were present in 28.4% and positive patch tests were found in 15.2%. The probability of contact sensitization was found to be independent of the number of positive prick tests, thus reiterating the need for combination testing in such patients.

Latex contact urticaria is a condition frequently seen in health workers. Clinically, symptoms range from contact urticaria to anaphylaxis and it is often associated with hand eczema and allergic contact dermatitis [8]. In a study of 1294 health-care workers, 295 patients with glove-induced symptoms were prick tested to latex as well as patch tested to rubber allergens. Twenty-seven (9.2%) of these patients were found to be positive to latex on prick testing and 31 patients (10.5%) exhibited positive patch tests to rubber-related allergens. The greatest frequency of positive readings were obtained from thiuram and carba mix, with 12 and nine positive responses, respectively. The authors recommended that all health-care workers with glove-related dermatitis undergo both prick and patch testing to detect delayed-type hypersensitivity to rubber chemicals [9]. In our own study, only nine out of 106 health workers referred had positive prick tests to latex. However, 50 patients subsequently went on to demonstrate delayed-type hypersensitivity, with nickel, cobalt, rubber and its additives being the most common allergens reported, demonstrating the importance of dual testing. In those patients who tested positive to rubber additives, all reactions were felt to be of current relevance. Although delayed-type hypersensitivity to NRL has been contentious, there was a positive reaction to this and other rubber additives in one patient with a 12-month history of gravitational eczema [10].

Chefs and housewives represent another subset of patients who often present with hand dermatitis. In a small study of food handlers in Sydney, 14 patients with hand dermatitis were patch and prick tested. In all patients, prick tests identified the food allergens of which seafood was the most frequently positive. Patch tests did not identify any of the food allergens [11]. In our own series only one patient had a positive prick test to cod with other positive reactions being to tomato and egg. Although one patient had a positive patch test response to an allergen in the bakery series, there were no other cell-mediated reactions to foods.

In a retrospective analysis of 873 food handlers with occupational allergic contact dermatitis [12], an increased rate of sensitization to nickel, thiuram mix, formaldehyde and compositae mix was demonstrated. Seven patients in our study group tested positive on patch testing to rubber additives and components of the rubber series as well as to nickel and PPD. Only one patient, however, had had a positive prick test to latex.

AD continues to be an increasing problem in the community. Patients often attribute flares to various food allergies with subsequent referral to secondary care. In our cohort of adult atopic subjects, 29 out of the 78 patients who were prick tested had positive immediate-type hypersensitivity to airborne allergens and foods with three such patients demonstrating clinical features in keeping with the oral allergy syndrome, a pollen-food cross-reaction syndrome in which oral symptoms are triggered by the ingestion of raw fruits/vegetables and nuts [13]. However, 56% of patients also demonstrated cell-mediated hypersensitivity with nickel cobalt, colophonium, fragrance mix and rubber additives being among the most common allergens.

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In the subset of atopic children, higher numbers of reactions were seen to prick tests. Five out of nine children also demonstrated positive results on patch testing to nickel, cobalt, fragrance and the medicament series. A study that looked at allergies in children aged 5–15 years analysed immediate- and delayed-type contact hypersensitivity to food and other allergens in 33 children with AD. Methods of allergen application included prick testing, patch scratch tests and the atopy patch test, where the European standard series was supplemented with foods such as cows milk, egg, peanut and soy. Foods were removed after 24 h. Results suggested that food allergy played only a limited role with just under half the children demonstrating positive reactions on patch testing [14]. Any child therefore with a persistent dermatitis irrespective of the clinical diagnosis should be considered for patch testing as the pattern of dermatitis does not predict the outcome [15].

Skin testing (patch testing, prick and intradermal testing) can also be helpful in determining the cause of drug reactions. Guidelines recommend investigation is undertaken 6 weeks to 6 months after complete healing of the drug reaction [16]. In our study, six patients were tested to local anaesthetic. Although no positive reactions were found on prick testing, four patients demonstrated delayed hypersensitivity to allergens thought to be of current relevance, including one to local anaesthetic. Our experience of investigating reactions to local anaesthetics is similar to others [17] with allergy being a rare cause of symptoms, but when it is delayed-type hypersensitivity reactions proven by patch testing is the most frequent cause. In general, where skin tests identify drugs as a cause of allergy, prick tests are positive in 23% (typically those with urticaria and angioedema), patch tests in 43% and intradermal tests in 67% (both immediate and delayed reactions) [16].

We propose that in individuals who present with contact urticaria, consideration should also be given to excluding a delayed-type hypersensitivity. In particular, patients with atopic eczema, suspected latex rubber allergy, hand dermatitis (particularly occupational) and drug reactions should be targeted to receive both investigations. We recommend that patients with suspected allergic skin disease be managed in an environment where investigation of both immediate- and delayed-type hypersensitivity, which conforms to published guidelines [1], can be undertaken.

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