

Retrospective evaluation of the consequence of alleged patch test sensitization

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The risk of actively sensitizing a patient in connection with diagnostic patch tests exists. This risk, however, is extremely low, especially from standard allergens, and if the test is carried out according to internationally accepted guidelines. This retrospective study investigates the clinical consequences in cases of possible patch test sensitization. Among 7619 consecutively tested eczema patients in a 14-year period 26 (0.3%) were identified in the database as having had a late patch test reaction, which may be an indication of patch test sensitization. 9 of these cases were not suitable or available for the follow-up investigation and 3 patients were not traceable. Among the 14 remaining patients 1 had a reaction to gold sodium thiosulphate, which was assessed to be a persistent reaction and not a late reaction, and in 2 patients a clear relevance for the late reacting allergen was found. For the remaining 11 patients we could not rule out that they were patch test sensitized, and they were investigated further. 1 was diseased and 10 were interviewed regarding the possible consequences of the alleged patch test sensitization. 9 had not experienced any dermatitis problems, and 1 could not exclude the possibility that the alleged patch test sensitization had aggravated her dermatitis problems, although we find it unlikely based on the full clinical history. Even though the patient material is small and the limitations inherent in such a retrospective study, the results and the literature indicate that development of clinical contact dermatitis following patch test sensitization is very rare.

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Diagnostic patch testing is an important tool for the evaluation of contact allergy and allergic contact dermatitis, but it carries the risk of active sensitization to a test substance. Patch test sensitization is by definition a negative patch test reaction followed by a flare-up after 10–20 days, and a positive reaction within few days of retesting with the allergen in question (1, 2). Active sensitization is a rare adverse event in relation to diagnostic patch tests, especially with standard series allergens, where the test concentrations have been optimized. It is commonly accepted that the diagnostic benefits of a properly performed patch test by far outweighs the risks, but it is important to be aware of the possibility of sensitization. The incidence and the consequences

of active sensitization are rarely reported, and they are the subject of this retrospective investigation.

Materials and Methods

In a 14-year period a total of 7619 consecutive patients have been patch tested at the Department of Dermatology, Odense University Hospital. The placing of the patch tests on the back is routinely carefully marked on the back skin by ink and drawn on paper. Routine reading is performed twice on D2–D3 and D5–D7. It is possible to register the occurrence of late reactions by ticking a box on the patient record, if such an event is registered by the patient or a doctor. The diagnostic patch test results are stored in a database, making retrieval of registered late reactions possible. The patients have been tested with a standard series encompassing the True Test panels 1 and 2 supplemented with petrolatum-based test materials applied for 2 days in Finn Chambers[®] on Scanpor. The identity

of the contact allergen causing a late appearing patch test reaction is attempted to be clarified, when possible, by repeated patch tests with the contact allergens suspected to be the culprit for the late reaction. The patients are not specifically encouraged to report reactions that appeared later than the usual reading days, but it is not unusual for patients to ask about sensitization risk.

Results

A total of 26 patients (0.3% of tested patients) in the Allergen Database (Langtved data AS, Odense, Denmark) are registered to have had a late reaction in the 14 years preceding 2005. In 9 of the patient records, the late reaction was not described adequately to be included in this analysis or the allergen responsible for the late reaction was not identified. The registration number of 3 patients was not recognized by the computer system and their records therefore not traceable. The remaining 14 cases of late reactions are evaluated in this report.

1 late reaction to gold sodium thiosulfate was concluded to be a persistent reaction in the patient record and not a late appearing reaction. In 2 patients, it was concluded that patch test sensitization was a less likely explanation for the late reaction, as clinical relevance was obvious by history and the contact allergy believed to be pre-existing. 1 of these patients had a late reaction to an acrylate to which the patient was exposed at her work place. The other had reactions to the textile dyes disperse blue 106 and 124, and the use of jeans was believed to be the source of sensitization.

The remaining 11 patients, all but one female, were sent a letter explaining the investigation and later interviewed by telephone in order to examine whether an active sensitization was likely to have caused clinical symptoms. The substances that caused late reactions that cannot be ruled out as a result of active sensitization are listed in Table 1. 9 of the patients had not observed any problems with the allergens in question and no worsening of their condition was experienced subsequent to patch testing. 1 patient (no. 3) who had had a late reaction to parthenolide, tansy and p-tert-butylphenol formaldehyde resin could not exclude that her condition had worsened following the test. She believed that her need to avoid contact with flowers and plants had increased. She had previous to the patch test had symptoms when doing gardening work, so whether the test was responsible for the worsening of her condition may be speculated. Moreover,

most of her symptoms were characteristic of type I allergy. 1 of the patients was diseased (no. 8).

6 of the patients had been retested with the allergens in question to confirm which allergen had caused the reaction, and all produced strong reactions within a few days. At retest, patient no. 4 additionally developed late reactions to epoxy resin, oxidized limonene and p-tert-butylcatechol. In 4 patients the late reactions appeared on D9 or D10 and might possibly have been true late reactions. 1 was a reaction to the corticosteroid tixocortol pivalate. Unfortunately, information about the day of appearance of the reaction was not available for the remaining patients. It was only possible to find the date of the reaction being registered at the clinic. Patients 1, 8, 10 and 11 had doubtful reactions to the late allergen within 7 days of testing, but not a positive reaction until later. This might be due to irritancy, but could also indicate that the allergy was pre-existing. No clear relationship between atopy or multiple allergies and late reactions was observed, although it should be noted that 4 of the patients had 3 or more positive reactions to other contact allergens. There were 2 cases of late reactions to p-tert-butylphenol formaldehyde resin and 1 to p-phenylenediamine (PPD) in the True Test panels, the others were to petrolatum-based preparations. A predominance of late reactions from plant extracts was seen. However, as mentioned, in patients 8, 10 and 11 the late reactions were preceded by doubtful positive reactions making active sensitization less likely.

Discussion

Late appearing patch test reactions have been reported for a wide range of contact allergens, that is, acrylates (3–5), methylchloroisothiazolinone (6, 7), phenylglycidyl ether (8), diaminodiphenylmethane (6, 8, 9), p-tert-butylcatechol (9), tetramethylthiuram monosulphide (9), corticosteroids (10–12), Compositae mix and sesquiterpene lactone mix (SL-mix) (13–15), PPD (16), chromium and cobalt (17, 18) and corticosteroids (10, 19). It is difficult to determine whether a late reaction is really caused by active sensitization. Retesting with the relevant allergen is a tool for evaluation of a possible patch test sensitization. If a positive reaction to a retest with the allergen develops within a few days, patch test sensitization is one of several possible explanations. However, this positive reaction could also be the result of exposure between tests, or perhaps pre-existing sensitization. True late reactions to textile dyes, budesonide, acrylates and

Table 1. Patients with a late reaction who were possibly patch test sensitized

Pt	Substances producing late reactions	Other contact allergies (standard series)	Day of registration of late reaction	Atopic dermatitis	Previous dermatitis	Current dermatitis	Years since late reaction	Confirming retest
1	p-tert-Butylphenol formaldehyde resin	No	D9 by the patient	No	Systemic skin disease	Mild	1½	No
2	Two unspecified components in the Compositae mix	Fragrance mix I and II Nickel	D21	No	Hand dermatitis	Recurring hand dermatitis	1½	Yes
3	Parthenolide	Nickel, Neomycin	D20	No	Periorbital dermatitis	Recurring periorbital dermatitis	2	Yes
4	Tansy extract p-tert-Butylphenol formaldehyde resin Compositae mix SL-mix Parthenolide	Compositae mix Parthenolide p-tert-Butylcatechol Fragrance mix I Cl-me-isothiazolinone Formaldehyde and releasers	D21	Yes	Hand dermatitis	Mild	4½	Yes
5	p-Phenylenediamine	No	D14	No	Unspecific dermatitis	Recurring outbreaks of dermatitis	6½	No
6	Tixocortol pivalate	No	D9 by the patient	Yes	Atopic dermatitis	No	8	No
7	Carvone	Fragrance mix I	Not known	No	Facial and hand dermatitis	Subacute cutaneous LE	9	No
8	Spearmint SL-mix	Neomycin Fragrance mix I, Primin Black rubber mix	D14	No	Subacute cutaneous LE Hand dermatitis	Patient is diseased	13	Yes
9	Primin	No	D21	No	Hand dermatitis	No	13½	Yes
10	Feverfew	SL-mix, epoxy resin,	D10	Yes	Facial, foot and hand dermatitis	Recurring facial, foot and hand dermatitis	11½	No
11	SL-mix	Compositae mix Colophony Fragrance mix I	D10	No	Hand dermatitis	No	13	Yes

Compositae allergens have been reported (10, 15, 20–22), and for instance gold sodium thiosulfate has produced flare-up reactions after D10 in subjects known to be allergic (23). This challenges the view of considering late reactions as evidence of active sensitization. Also, patch test reactivity may fluctuate significantly between tests due to technical as well as immunological variations (24). A weak contact allergy that did not generate a positive reaction in the first test might be boosted and produce a positive reaction in a subsequent test. Reactions that were doubtful in the first test and strongly positive in the second test, and vice versa, have been described (14).

Few consecutive studies have attempted to record patch test sensitization. Bygum (25) patch tested 103 patients with the True TestTM standard series and included a reading on D21. She found no reactions appearing after D7 and therefore no indication of active patch test sensitization. However, 17% of positive reactions were persistent and still positive on D21. In a few studies without a reading after D7, but where the patients were tested twice or more and the number of new positive reactions was registered, no link between the new reactions to patch test sensitization was believed to exist. In 2 separate studies by Hindsén and Johnke (24, 26), no association was found between the number of patch test procedures performed and the development of nickel reactivity. Meneghini (27) reported that 55 of 309 patients had new positive reactions after having been patch tested twice with a series of 31 allergens. He concluded that the most plausible explanation was further environmental exposure rather than patch test sensitization or fluctuations in the strength of reactions. We have reported the course of positive reactions in 264 patients tested twice with the True TestTM, and the larger number of new positive reactions found compared to lost positive reactions was explained by the selection of patients tested. Those tested twice are often individuals with multiple allergies and ongoing dermatitis problems, and it may seem likely that the high frequency of new positives in such a group of patients reflects a heightened susceptibility to develop delayed-type hypersensitivity (28). In a study of 4386 consecutively tested patients, Paulsen (15) reported no clear indication of active sensitization in patients routinely patch tested with SL-mix. Based on SL-mix reactivity or clinical suspicion, 549 patients were also tested with Compositae mix. A total of 4 late reactions were seen, but the clinical picture and patient history suggested that sensitization was pre-existing. Some patients have been tested on

several occasions and new allergies have been discovered over time. Whether the new allergies are sensitizations from previous patch testing or reflect cross-reactivity or environmental exposure is unclear.

Patch test sensitization was on the other hand believed to be the explanation for late reactions in other studies. Wilkinson and Pollock (13) concluded that the SL-mix in combination with the Compositae mix exceed a critical level of exposure and present a significant sensitization risk. 576 consecutive patients were tested with both SL-mix and the Compositae mix. 4 patients returned with late reactions, although more possibly occurred, as many patients may not have presented themselves spontaneously. 1 had a reaction to Compositae mix, 2 had reactions to both mixes and 1, who was previously tested positive to Compositae mix, a reaction to the SL-mix. The authors suggested the use of the SL-mix in the standard series and Compositae mix for aimed testing, which seems to be safe according to a later Danish study (15). Devos tested 2058 patients with PPD and 7 developed a late reaction without relevance, suggesting active sensitization. He concluded that PPD should not be included in the standard series because it is a strong sensitizer giving rise to patch test sensitization (16).

Only few investigators have looked at the possible clinical relevance of late reactions. Agrup (17) retested 379 hand eczema patients with 11 substances first applied 6–21 months previously. In 74% of patients the results were unchanged, in 19% tests had become positive, in 5% negative, and in 2% some had become positive and others negative. Of the 79 patients who had possibly been sensitized, it was concluded that the clinical course of the hand eczema was unaffected. Calnan (18) collected 43 patients who had had late reactions during a 10-year period and they were retested. 37 of 47 substances that had produced a late reaction in the patients were positive. He reported that 2 patients developed clinical symptoms after having been sensitized by patch testing to a rubber chemical.

Studies indicate that the incidence of patch test sensitization is low, especially for the standard series allergens, where the test concentration has been optimized. One exception is possibly PPD that have been suggested to possess significant patch test sensitization potential (16, 29); however, we have only 1 case reported among more than 7000 consecutively patch tested patients. There is an ongoing scientific discussion on whether PPD should be removed from the standard series because of sensitization hazard. Having a screen for hair dye allergy *versus* the

risk of active sensitization is being debated, not helped by the difficulty of determining the actual patch test sensitizing potential of PPD (29–31).

This retrospective study exposes the difficulties that exist in investigating the incidence and especially the consequences of patch test sensitization. First, it is problematic to ascertain whether a late reaction is the result of active sensitization. The possibility of a late reaction being fluctuations in reactivity or boosting of an allergy complicate the matter and, as mentioned, true late reactions from several allergens have been reported. It must be emphasized that Table 1 lists the patients who have had late reactions, disregarding the cause. Second, in 14 years only few late reactions were registered at our clinic. From another study we know of a few patients with late reactions to plant extracts who were not registered in the database; thus the registration of late reactions is incomplete. Also, most patients will probably note if they develop an itchy spot on the back some weeks after a patch test procedure, but many, perhaps, will not report it.

The occurrence of 26 registered late reactions recorded among 7619 consecutively patch tested eczema patients is a minimum figure and we can only speculate how many unreported late reactions there have been in the study period. We found 1 patient who could not rule out that she had experienced a worsening of clinical symptoms after having had a late reaction. However, we do not find it likely that it is related to her late reactions. 8 patients had not experienced any dermatitis related to the allergens to which they had had late reactions. Some patients still had eczema but with no relationship to the allergens in question. It is a retrospective study and only limited conclusions can be drawn about the clinical consequences of patch test sensitization. However, these data and the literature indicate that subsequent allergic contact dermatitis following an alleged patch test sensitization is very rare in agreement with Etain Cronin's statement in her text book from 1980 (32).

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