

The Importance of Checking for Delayed Reactions in Pediatric Patch Testing

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Abstract: Patch testing is often performed with the final reading being completed at 72 hours. Studies in adults have shown that performing an additional reading several days later increases the yield of relevant positive reactions. We report a study of this matter in children. We conducted a prospective patch test study of 38 affected children aged 6 to 17 (mean 11.6 years), with presumed allergic contact dermatitis between April and July 2009. The patients were required to return at 48 hours for patch test removal and assessment of early reactions, at 72 to 96 hours (3–4 days) for evaluation of delayed reactions, and again at 168 to 216 hours (7–9 days) for a final late delayed reading. We tallied the number of patients with “equivocal” (+/?), +, ++, and +++ reactions and noted these as potential positive reactions by reading date. Twenty-five of the 38 children (66%) had a positive reaction at 48 hours; 32 children (84%) had a positive reaction at 72 hours (day 3); 19 children (50%) had a positive reaction at 168 to 216 hours (day 7–9). Of those 19, 16 (42%) had persistent reactions, while 5 children (13%) had new late delayed reactions. Among the new late delayed reactions, there were six allergens identified, four of which were considered of probable clinical relevance. When patch testing with Thin Layer Rapid-Use Epicutaneous test panels, a delayed reading beyond 72 hours may be needed to identify the offending agent(s) responsible for allergic contact dermatitis in some children. Additional studies are needed to assess optimal readings schedules.

Contact dermatitis is a common clinical problem in children. As in adult populations, the irritant type is the most prevalent. Allergic contact dermatitis (ACD) in children has been well recognized internationally for the better part of the last two decades (1). More recently, several studies have shown that ACD in children is more common in the United States than previously appreciated (2,3).

Allergic contact dermatitis is a T-cell mediated delayed hypersensitivity reaction in which reexposure of the skin to a recognized allergen in a previously sensitized person leads to a complex reaction involving lymphocyte proliferation and release of inflammatory mediators, which clinically manifests as dermatitis. After reexposure, these effects often begin within 12 to 24 hours, typically peak at 3 to 5 days, and may last up to

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4 weeks if left untreated (4). Patch testing is the diagnostic tool to evaluate ACD. In adults, the standard protocol is to remove the patch tests after 48 hours followed by a delayed reading at 72 to 96 hours (day 3–4) after application. Notably, late-delayed positive reactions appearing at 168 to 216 hours (day 7–9) have been reported in adult populations to have clinical relevance (5–7,14).

Cross-sectional surveys among dermatologists and allergists show that 52% of dermatologists and 48% of allergists perform both a 48- and 72- or 96-hour reading, while 26% of the dermatologists and 33% of the allergists performed a single reading at 48 or 72 hours (8,9). However, multiple studies in adults have shown that relevant positive patch test reactions may first appear after 72 (6,7) or 96 hours (5).

The purpose of this study was to prospectively examine the frequency and relevance of positive reactions at different time intervals and to check for late delayed patch-test reactions in children. We studied the percentage of positive reactions at 3 time intervals: 48 hours (early); 72 hours (delayed); and 168 to 216 hours (late delayed) among 38 children referred for patch testing.

MATERIALS AND METHODS

Approval for this study was obtained from the University of California, San Diego, and Rady Children's Hospital institutional review boards. Included were 38 children (21 girls and 17 boys) aged 6 to 17 years (mean 11.6 years) who were referred by pediatric dermatologists for a high clinical suspicion of ACD. Patients who were excluded from the study consisted of children with: very severe dermatitis with no area on the back or upper extremities to test; history of use of immunosuppressive medications, systemic corticosteroids, or use of topical corticosteroids to the test area within 7 days of testing; ultraviolet light or tanning treatments within 3 weeks of testing; and pregnant patients.

The patients underwent patch testing at the Pediatric and Adolescent Contact Dermatology Clinic at Rady Children's Hospital between April and July 2009. Testing was conducted with the Thin Layer Rapid-Use Epicutaneous test (T.R.U.E. TEST, panels 1.1, 2.1, 3.1), which included 29 composite allergens (including the negative control). These materials were obtained from Allerderm Laboratories (Phoenix, Arizona). The tests were applied to the back and reinforced with Hypafix[®] tape (Smith and Nephew, Inc., Largo, Florida). Patients were instructed to keep their backs dry and to avoid sweating during the period the patch tests were in place. After 48 hours, patch tests were removed, and an early reading was performed. A delayed reading was

performed at 72 hours (3 days after test application). A late-delayed reading was subsequently performed between 168 to 216 hours (7–9 days after application).

The strength of the reactions was graded on the International Contact Dermatitis Research Group (IC-DRG) grading scale with a maximum intensity of + + + (10). Patients with +/? ("equivocal"), +, + +, and + + + reactions at any of the reading intervals were tallied as a positive reaction for the purpose of calculating positivity rate. Reactions were assessed by the contact dermatitis specialist and investigated for clinical relevance, as per previously described relevance assignment protocols (4). *Probable* relevance, for example, was assigned if patients were found to have these chemicals currently in their environment and improved with avoidance.

RESULTS

Twenty-five of the 38 children (66%) had a positive reaction (+/?, +, + +, + + +) at 48 hours. Of these, 10 children (26%) had reactions that resolved by 72 hours and were thus considered to be likely irritant (not allergic) in nature. The most common irritants were potassium dichromate, carba mix, and diazolidinyl urea. Thirty-two children (84%) had a positive reaction at 72 hours (day 3), while only 19 children (50%) had a positive reaction at 168 to 216 hours (day 7–9). At the 7- to 9-day interval, 16 of those 19 patients (42%) had reactions that had been detectable at 72 hours and had persisted to the later interval, while 5 children (13%) had new late delayed reactions. Three of the patients who had persistent reactions also had new late-delayed reactions. Six allergens with late-delayed onset occurred, four of which were considered of *probable* relevance (Table 1).

Limitations

This study was limited by the small number of patients, the small number of allergens, and the referral bias,

TABLE 1. Patch Test Reactions Developing After 72 Hours in 5 Children

Allergen	Number of positive reactions	Strength of positive reactions	Relevance
Quaternium 15	1	+	+
Formaldehyde*	2	+; + +	+
Diazolidinyl urea	1	+	+
Epoxy resin*	1	+ +	–
Neomycin sulfate	1	+/?	–
p-tert-butylphenol	1	+	+
formaldehyde resin*			

*One patient had 3 reactions develop after 72 hours.

because all patients were referred with a high index of suspicion for ACD. The T.R.U.E. test was used in this study, and the results do not necessarily apply to patch testing with the same allergens in other vehicles or concentrations. Finally, our study utilized a second reading at 72 hours. A larger study with second readings performed at 96 to 120 hours would better assess how often third readings in the 7- to 9-day range are required.

DISCUSSION

To our knowledge, this is the first report of late-delayed reactions in pediatric patients from a North American contact dermatitis referral center. Adult studies have repeatedly demonstrated the utility of a late delayed reading beyond 72 (6,7) or 96 hours (5), with the most likely additional allergens detected being metals and topical antibiotics (5). Our pilot data suggests the importance of evaluation for late-delayed reactions in children as well. The six allergens we noted to cause late-delayed readings were formaldehyde, quaternium 15 (Q15), diazolidinyl urea, p-tert-butylphenol formaldehyde resin, neomycin sulfate, and epoxy resin. Of note, the formaldehyde, the two formaldehyde-releasing preservatives (diazolidinyl urea and Q15), and the formaldehyde adhesive (p-tert-butylphenol formaldehyde resin) were found to be of *probable* relevance, as patients were found to have these chemicals currently in their personal products, and their clinical manifestations improved with avoidance. These six allergens are among a large number of allergens that have previously been observed to cause late-delayed reactions in adult patch testing performed with traditional petrolatum or aqueous vehicles (6,7).

Our study confirms the repeated finding of the importance of contact allergy to formaldehyde-releasing preservatives (FRPs) in children (2,3,10,11). These are widely used in skin care products marketed for both adults and children (12). Quaternium 15, the most sensitizing of the FRPs, has been found to cause clinically relevant reactions in 9.3% of 4,910 patients patch tested by the NACDG from 2001 to 2002 (13), and 4% of the 100 children in the Hogeling and Pratt study (11). Notably, Zug et al placed Q15 among the top six allergens in children, as they found that 3.6% of patients under the age of 18 had clinically relevant reactions (2).

We conclude that the importance of detecting late-delayed relevant allergens cannot be overstated. Patch

test practitioners using the T.R.U.E. test in pediatric populations should be aware of the potential for late-delayed relevant reactions first appearing after 72 hours, especially to formaldehyde-related allergens, as this is critical for the patient and parents to implement avoidance.

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