

Extreme patch test reactivity to *p*-phenylenediamine but not to other allergens in children

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Summary

Background. According to clinical impression, extreme patch test reactions (+++) to *p*-phenylenediamine (PPD) are not uncommon in children.

Objectives. To investigate the patch test reactivity in children (aged 1–14 years) in comparison with other age groups and other allergens.

Methods. A retrospective analysis was performed of data from the German Information Network of Departments of Dermatology, including all patients consecutively patch tested between 1994 and 2004 with PPD, and, for comparison, nickel, fragrance mix I, and methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI). The distribution of +, ++ and +++ grades of positive reactions among those with a positive reaction were analysed in five age strata.

Results. We found a strikingly higher proportion of +++ reactions to PPD in children than in all other age groups ($p < 0.001$). No such difference was observed for the other allergens. The main suspected exposures associated with extreme reactions to PPD in children were hair dyes and 'henna tattoos'.

Conclusions. The high proportion of extreme patch test reactions to PPD, but not to other important allergens, in children reflects intense sensitization, probably because of a high induction dose from PPD-containing 'henna tattoos'. In children with a history of contact allergy to 'henna tattoos' or hair dyes, the standard patch test concentration of PPD 1% should be drastically reduced.

Key words: children; *p*-phenylenediamine; patch test.

According to clinical impression, extreme positive patch test reactions (+++, erythema, infiltration, and coalescing vesicles, according to the classification of the International Contact Dermatitis Research Group) to *p*-phenylenediamine (PPD) are not infrequently observed in children. This phenomenon may result

from a sensitizing exposure with a high induction dose per area (1), namely, 'henna tattoos' adulterated with PPD. To verify this impression empirically, we analysed data from the Information Network of Departments of Dermatology (IVDK; www.ivdk.org) concerning the patch test reactivity of children aged 14 years or younger without occupational exposure to PPD in comparison with other age groups.

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Methods

The IVDK has been described elsewhere (2, 3). For the current analysis, all patients consecutively patch tested between 1994 and 2004 with PPD 1% in petrolatum, and, for comparison, nickel sulfate (5%

pet.) and fragrance mix I (8% pet.) as the most common allergens, and methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) 0.01% aqua as an allergen with similar potency as PPD (4), were included. After 2004, PPD 1% was no longer present in the German baseline series.

The prevalence of positive reactions to the four allergens, and the distribution of +, ++ and +++ grades of positive reactions among those with a positive reaction, were analysed in five age strata (Tables 1–4). The homogeneity of the share of +++ reactions across all age strata was tested with the chi-square test. In cases of significant heterogeneity, the youngest age group was compared with each other age group, resulting

in a total of three *post hoc* pairwise comparisons in terms of a closing test procedure. The *p*-values were alpha adjusted according to the Bonferroni method (total number of statistical tests: $n = 5$). *p*-Values of <0.05 were considered to be statistically significant. For data management and analysis, the statistical program package SAS (version 9.2; SAS Institute, Cary, NC, USA), was used, with adherence to published guidelines (5).

Results

As shown in Table 1, the prevalence of positive patch test reactions to PPD in children aged 14 years or younger was 2.36% – lower than in any other age group. However,

Table 1. Frequency of positive reactions and distribution of different grades of positive reactions in different age groups for *p*-phenylenediamine (PPD) (1% pet.) in patients patch tested in the Information Network of Departments of Dermatology, 1994–2004

Age group (years)	Tested	Patch test reactions to PPD			
		% positive	% + of positive	% ++ of positive	% +++ of positive
1–14	1270	2.36	43.3	13.3	43.3
15–30	19 038	3.81	51.1	30.3	18.6
31–44	21 321	4.30	53.2	29.7	17.1
45–60	25 904	5.17	57.8	28.4	13.8
61+	23 284	4.22	61.1	29.3	9.6

There was significant heterogeneity of the distribution of +/++ versus +++ reactions. In *post hoc* pairwise comparisons, there was a significant difference between the youngest and all older age groups regarding the proportion of +++ reactions among all positive reactions.

Table 2. Frequency of positive reactions and distribution of different grades of positive reactions in different age groups for nickel sulfate (5% pet.) in patients patch tested in the Information Network of Departments of Dermatology, 1994–2004

Age group (years)	Tested	Patch test reactions to nickel sulfate			
		% positive	% + of positive	% ++ of positive	% +++ of positive
1–14	1290	12.7	57.3	31.1	11.6
15–30	19 021	22.9	45.8	41.7	12.5
31–44	21 308	22.0	42.9	41.6	15.5
45–60	26 265	11.6	53.7	35.7	10.6
61+	23 610	6.7	63.6	29.2	7.2

There was significant heterogeneity of +/++ versus +++ reactions. In *post hoc* tests, there was no significant difference regarding the proportion of +++ reactions between the youngest and all other age groups.

Table 3. Frequency of positive reactions and distribution of different grades of positive reactions in different age groups for fragrance mix I (8% pet.) in patients patch tested in the Information Network of Departments of Dermatology, 1994–2004

Age group (years)	Tested	Patch test reactions to fragrance mix I			
		% positive	% + of positive	% ++ of positive	% +++ of positive
1–14	1276	7.45	85.3	12.6	2.1
15–30	19 085	6.88	68.3	26.7	5.0
31–44	21 348	9.65	64.6	27.7	7.7
45–60	25 904	12.5	64.3	27.9	7.8
61+	23 364	14.3	66.6	26.9	6.5

There was significant heterogeneity of +/++ versus +++ reactions. In *post hoc* tests, there was no significant difference regarding the proportion of +++ reactions between the youngest and all other age groups.

Table 4. Frequency of positive reactions and distribution of different grades of positive reactions in different age groups for methylchlorisothiazolinone/methylisothiazolinone (MCI/MI) (0.01% aqua) in patients patch tested in the Information Network of Departments of Dermatology, 1994–2004

Age group (years)	Tested	Patch test reactions to MCI/MI			
		% positive	% + of positive	% ++ of positive	% +++ of positive
1–14	1279	2.19	78.6	21.4	0
15–30	18 811	1.40	68.4	27.8	3.8
31–44	21 235	2.62	61.2	30.5	9.3
45–60	25 760	2.81	64.2	29.7	6.1
61+	23 234	2.47	71.7	23.6	4.7

There was significant heterogeneity of +/++ versus +++ reactions. In *post hoc* tests, there was no significant difference regarding the proportion of +++ reactions between the youngest and all other age groups.

Table 5. Suspected allergen source in children aged 14 years or younger with +++ reactions to *p*-phenylenediamine, patch tested in the Information Network of Departments of Dermatology, 1994–2004

Category of suspected allergen source	No. of positive	No. of +++	% of positive	% of +++
Hair dyes, tattoos	11	10	90.9	76.9
Cosmetics, creams	5	1	20	7.7
No information	5	2	40	15.4
Other	9	0	0	0
Total	30	13	43.3	100

in children, a strikingly higher proportion of +++ reactions, amounting to 43% of all positive reactions, was observed. This was highly significant as compared with all older age groups ($p < 0.001$). With increasing age, the prevalence of PPD contact sensitivity gradually became higher (with the exception of the group '61 years and older'), predominantly because of + reactions. With regard to nickel and fragrance mix, the percentage of total positive reactions was also lower in children, but showed a proportion of + reactions similar to, or greater than, that in other age groups (Tables 2 and 3). MCI/MI showed a somewhat peculiar distribution across the age groups; however, in children, not a single +++ reaction was observed (Table 4).

In 11 of the 30 children who reacted to PPD, hair dyes and tattoos were suspected as causative allergens for contact sensitivity. Ten of these 11 children showed +++ reactions, accounting for 77% of all +++ reactions to PPD (Table 5). This proportion of +++ reactions was significantly higher than in the combined remaining exposure profiles.

The characteristics of 13 children who showed extreme (++++) positive reactions to PPD are shown in Table 6. Severe reactions were predominantly associated with

scalp dermatitis, exposure to hair dyes or tattoos, and dermatitis of the arms. Five of 6 children tested with the hairdressers series had +++ reactions to PPD. In the 17 children with weaker reactions, more variable sites of contact dermatitis were documented. In only 2 cases was face (not scalp) dermatitis observed, and in two more dermatitis on the arms, the hands being the most frequently affected site (4 of 17).

Comment

In this study, both the frequency and the intensity of sensitization to PPD in the youngest age group (1–14 years), as compared with older patch-tested patients, were analysed. The prevalence (2.36%) was lower than in older age groups, but nevertheless high enough to be regarded as a warning signal. Obviously, children are already exposed to PPD and similar dye compounds. Being sensitized to PPD will have implications for the future occupational career – the more so as the intensity of sensitization is high in a large proportion of children. This has also been reported by other groups (6, 7). The degree of sensitization depends, among other things, on the induction dose (1). It has been shown that henna tattoos, one important cause of sensitization to PPD in children, may contain >15% PPD (8). In historical sensitization experiments (human maximization test), all subjects ($n = 24$) exposed to 10% PPD were sensitized (9).

Therefore, it is not surprising that children often show unacceptably strong patch test reactions to PPD at the recommended patch test concentration of 1% pet., especially after sensitizing exposure to so-called temporary black 'henna' tattoos. It should be noted that henna itself is a weak allergen, and that sensitization is caused by PPD, which is added to henna powder to increase the intensity of the colour. Many reports have addressed the severity of clinical

Table 6. Characteristics of *p*-phenylenediamine-allergic children with +++ reactions

Patient	Age (years)	Sex	Category of suspected allergen source	Site of contact allergy	Specific series tested in addition to baseline series
1	13	F	Hair dyes	Scalp	Hairdressers
2	13	F	Hair dyes	Face	Hairdressers
3	13	F	Hair dyes	Scalp	Hairdressers
4	12	F	Hair dyes	Scalp	Hairdressers
5	14	M	Hair dyes	Scalp	Hairdressers
6	6	F	Tattoos	Arms	Textile dyes, henna paste
7	5	M	Cosmetics, creams	Arms	Baseline only
8	9	F	Tattoos	Arms	Baseline only
9	11	M	Tattoos	Arms	Baseline only
10	12	M	No information	Feet	Leather allergens
11	6	M	Tattoos	Trunk	Baseline only
12	10	M	Tattoos	Generalized	Baseline only
13	8	M	No information	No information	Textile dyes

F, female; M, male.

reactions in children and adolescents previously exposed to temporary henna tattoos or hair dyes (6, 10–14). However, to the best of our knowledge, the strength of patch test reactions to PPD exclusively in children has not been systematically studied. We aimed at quantifying this case-by-case observation by analysing routine clinical surveillance data, in particular by comparing the proportion of +++ reactions to PPD (i) between children (aged ≤ 14 years, and thus with no occupational exposure) and older age groups, and (ii) with the proportions observed for the two most common allergens in children, namely, nickel and fragrance mix, and MCI/MI, an important allergen of similar potency as PPD, according to local lymph node assay results (4).

We showed that the proportion of +++ reactions among all positive reactions was strikingly, and significantly, higher (43.3%) than in any other age group. In 11 patients (37%), dye compounds, predominantly hair dyes and 'henna tattoos', were suspected as causative allergens, and these accounted for the vast majority of +++ reactions to PPD (10 of 13 children). Accordingly, all 5 cases of face and scalp dermatitis, with hair dyes as the culprit exposure, showed strong reactions to PPD, comprising 5 of 13 of +++ reactions to PPD in children. Another common anatomical site associated with +++ reactions to PPD was the arm, associated with previous application of 'henna tattoos', which was noted as the culprit exposure in 5 cases. In this context, it must be mentioned, however, that 'culprit exposures' refer to exposures that are relevant for a current episode of contact dermatitis leading to patch testing, and do not preclude the possibility that, for example, 'henna tattoos'

may have been applied, and caused sensitization, earlier in some of the children currently exposed to hair dyes.

In order to address a possible age-dependent reaction pattern of patch test reactions in children, we performed the same analysis for three other common allergens in children, namely, nickel, fragrance mix, and MCI/MI. For these allergens, we were not able to show a significant difference in the proportion of +++ versus + and ++ reactions between children and other age groups. In contrast, in patients aged 14 years or younger, + reactions to these three allergens seemed to be more frequent. Therefore, we assume that the high proportion of +++ reactions to PPD in children in our data does not indicate a general tendency of children to develop extreme reactions, but reflects the intensity of sensitization to, mainly, 'henna tattoos', which are known to cause severe clinical disease pictures in this age group. Moreover, MCI/MI, as an allergen of similar potency, did not elicit +++ reactions in this age group. Thus, exposure conditions [frequency of application (per time unit), duration, dose/area, possible co-factors] and the induction dose seem to drive the phenomenon that we observed, and not potency alone.

Interestingly, in the other age groups (except for the oldest one), the prevalence of contact sensitivity to PPD was gradually rising, probably reflecting increasing occupational and non-occupational exposure to hair dyes. In a recent analysis of the IVDK data, these two exposures accounted equally for the majority of 56% identifiable causes of contact allergy to PPD (15). In this study, the prevalence of contact dermatitis caused by PPD was 4% in patients, and extrapolated to 1% in the general population. Other investigators found an even higher prevalence of PPD contact allergy,

for example in 2.7% of the normal adult population of Thailand (16). Data on the frequency of contact allergy to PPD in children referred for patch testing are available from several large studies, and show a prevalence of approximately 2% in children up to 12 years old (17), and of 2–4%, when adolescents are included (18–20). This corresponds to the prevalence of 2.4% in our study. Some studies from the UK and Turkey reported an exceptionally high frequency of positive patch test reactions to PPD in children (21, 22), of up to 9% (23). However, because of different patient referral characteristics and, probably, different typical exposures, the results of clinical series from different countries are difficult to compare.

PPD contact allergy in the IVDK data has been shown to be associated with specific exposure patterns. It was as frequent in clients as in hairdressers (24, 25), and PPD was found to be the main causative allergen in face and scalp dermatitis (26), where it also elicited significantly stronger patch test reactions than at other sites of contact dermatitis (15). Our sub-analysis in children is in accordance with these findings, showing extremely strong (+++) patch test reactions to PPD after exposure to both hair dyes and henna tattoos. A recent analysis of undesired events caused by hair colouring products notified to the cosmetovigilance schemes of several cosmetic companies revealed that a history of previous henna tattoos was a major risk factor for the severity of allergic contact reactions (27). However, regardless of the initial sensitization process, hair dyes seem to be of growing importance as a major allergen source for the elicitation of non-occupational PPD contact allergy. Patients with stronger patch test reactions to PPD were more likely to report a history of hair dye reaction and were less likely to continue dyeing their hair (13). In another study from the UK, an increasing frequency of patch test reactions to PPD was reported over 6 years, with only a minor proportion being attributable to henna tattoos (28). According to interview-based studies in the Danish population, a major proportion of cases with severe scalp dermatitis caused by hair dyes were not referred to a dermatologist, and many cases might therefore not be adequately diagnosed (29). In the most recent study from Denmark, hairdressing apprentices and matched controls had dyed their hair for the first time at the ages of 12.1 and 13.3 years, respectively (30). Thus, this also seems to be a relevant exposure source for PPD in children, which is supported by our findings.

Limitations of our study are the small absolute number of PPD-positive tested children, despite the overall large clinical sample and the availability of data concerning

only current, but not initial, allergen exposure. Therefore, we could not exclude prior sensitization through 'henna tattoos' in children tested with PPD for other reasons; thus, the extreme patch test reactivity to this compound might be attributable to overrepresentation of 'henna tattoo' reactors. However, the importance of oxidative hair dyes for elicitation of contact dermatitis that we observed, beyond the well-known, but probably non-exclusive, role of 'henna tattoos', is also in accordance with our previous observation that, in adults with face and scalp dermatitis, patch test reactions to PPD after non-occupational exposure to hair dyes are significantly stronger (15).

In conclusion, our study provides evidence for the relevance of 'henna tattoos' and also of hair dyeing as the main causative exposures leading to intense PPD contact allergy in children aged 14 years and younger. A significantly higher proportion of +++ patch test reactions to PPD – but not to other allergens – than in older age groups appears to reflect the intensity of sensitization to this compound. As children did not exhibit a specific pattern of patch test reactivity in general, this points to a high induction dose of PPD, most probably through 'henna tattoos'. Therefore, our findings lead us also to conclude that patch tests with PPD at the standard concentration in patients aged 14 years or younger should be performed with extreme caution. Before testing young children with PPD, it is necessary to obtain information on not only actual but also previous exposure to the allergen sources of PPD mentioned above. In children with a clear history of allergy to hair dyes or exposure to 'henna tattoos', the standard concentration of PPD 1% should be severely reduced. According to our clinical experience, we even suggest that a titration test should be performed, starting at concentrations as low as 0.01%. A similar procedure has been previously proposed, based on a case series referring to adult patients with a history of temporary henna tattoos (14). Hair dyeing in children using PPD and related dyes is categorically to be discouraged.

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