

# Positive relationship – intensity of response to *p*-phenylenediamine on patch testing and cross-reactions with related allergens

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## Summary

**Background.** Hair dye exposure is the most common cause of sensitization to *p*-phenylenediamine (PPD). Cross-reactions with structurally related allergens occur.

**Objectives.** It is suggested that a stronger patch test reaction (3+ rather than 1+) to PPD (usually tested as 1% petrolatum) is associated with an increased propensity for cross-reactions. In this article we will demonstrate this association.

**Methods.** Of 230 patients with allergic reactions to PPD on patch testing identified during 2007–2012 from clinical records, notes for 221 were available for review. Data were collected regarding age, sex, and grade of reaction [International Contact Dermatitis Research Group (ICDRG) criteria] to PPD. Cross-reactions with the following allergens, found in our baseline series, were recorded: Disperse Yellow 3, *N*-isopropyl-*N'*-phenyl-*p*-phenylenediamine (IPPD), and caine mix. Having excluded 23 doubtful reactions, the reactions from 198 patients were further considered.

**Results.** Of the patients, 75.3% ( $n = 149$ ) were female, and the mean age was 48.6 years (12–82 years). Of the patients allergic to PPD, 16.6% ( $n = 33$ ) showed cross-reactions with one or more related allergens. Cross-reactions were seen in 16% with a grade of 1+, 14.5% with a grade of 2+, 28.6% with a grade of 3+ when PPD was tested 1% pet., and 50.0% when PPD was tested at 0.1–0.001%, arbitrarily considered to be 4+ ( $p = 0.02$ ; Cramér's  $V = 0.23$ ).

**Conclusion.** An increasing likelihood of reactions to Disperse Yellow 3, IPPD or caine mix was seen with increasing strength of patch test reaction to PPD. The clinical relevance of these cross-reactions is unclear.

**Key words:** contact allergy; cross-reactions; PPD; *p*-phenylenediamine; reaction strength.

*p*-Phenylenediamine (PPD) is an aromatic amine that is commonly used in hair dye. PPD is a precursor that is coupled and oxidized to produce colour (1). Hair dyeing is the most common route of sensitization to PPD (2), and

it is seen both in individuals administering the dye and in those receiving it. It has been observed that many severe reactions to PPD are associated with so-called 'temporary black henna tattoos' (2).

Rates of PPD sensitivity have been reported to range from 2.8% to 7.1% (1, 3, 4). Over the past 30 years, these rates have been increasing, reaching the upper limit stated above. This may be attributable to an increasing number of people using hair dye. It is also important to note that an increasing proportion of those dyeing their hair do so at a younger age, which increases their exposure over time (5, 6). In 2005, Ho et al. reported that those using hair

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dye were more likely to show strong patch test reactions (2+ and 3+) (7).

Clinically, it is important to understand the spectrum of severity of allergic contact dermatitis caused by PPD. Typically, the allergic contact dermatitis is a localized exudative erythema or a more widespread erythema multiforme-like eruption. Reactions to PPD can present as a severe bullous contact dermatitis. It is of note that there have also been reports of cases resembling angioedema (8) and even facial erysipelas, both of which have required alternative treatments to those used for allergic contact dermatitis.

When these severe reactions occur, it has been noted that cross-reactions with other dyes, local anaesthetics and an antioxidant in black rubber, *N*-isopropyl-*N'*-phenyl-*p*-phenylenediamine (IPPD), are more common. This is thought to result from similarities in the chemical structures of the allergens. It is suggested that a stronger patch test reaction (3+ rather than to 1+) to PPD (usually tested as 1% petrolatum) is associated with an increased propensity for cross-reactions (9–11). We performed a retrospective analysis of 6130 patch tested patients to qualify the belief that the relationship between strength of reaction to PPD and cross-sensitivity of structurally related allergens exists.

## Methods

### Patients and methods

We performed a retrospective analysis of patients presenting to our cutaneous allergy clinic at St John's Institute of Dermatology, London, between January 2007 and December 2012. Over the period, 6130 records were identified, and we found 230 patients who had reactions to PPD on patch testing over the 5-year period. Only 221 patient notes were available for review.

A chart review was performed, and the data collected included age, sex, history of hair dye use, and grade of reaction to PPD. Reaction grades were documented according to the International Contact Dermatitis Research Group (ICDRG) criteria: ? (doubtful reaction), 1+ (weak non-vesicular reaction), 2+ (strong oedematous/vesicular reaction), and 3+ (extreme reaction; bullous reaction) (12). We also included 4+ when PPD was tested at dilute concentrations (0.01–0.001%), to avoid extreme responses in high-risk patients. In these cases, all positive reactions were considered to be equal.

Patients with 1+, 2+, 3+ and 4+ reactions were considered to be sensitive/allergic to PPD. We excluded from analysis patients who had doubtful reactions. For the patients sensitive to PPD, reactions to the following aromatic amines in the European baseline series were also

recorded: 1% Disperse Yellow 3 (DY3), 0.1% IPPD (both from Trolab<sup>®</sup>, Reinbeck, Germany) and 10% caine mix III (benzocaine, dibucaine hydrochloride, and tetracaine hydrochloride (Chemotechnique Diagnostics, Vellinge, Sweden).

### Statistical analysis

Data are presented as a total of 198 (excluding 23 doubtful reactions), unless otherwise stated. For quantitative data, chi-square  $2 \times 2$  and  $2 \times 4$  contingency tables were used to show the difference in proportions when  $\leq 20\%$  of data cells had an expected frequency of  $<5$  but not 0. For all other cases, Fisher's exact probability test was used. A *p*-value of  $<0.05$  was considered to be statistically significant. As a test for linear association, Cramér's *V*-measure of association was used. A result of  $> 0.1$  suggests a substantive association between variables. Chi-square analyses and Fisher's exact probability testing were performed with VASSARSTATS online software (<http://vassarstats.net/>) (2013).

## Results

### General demographic data

One hundred and ninety-eight patients sensitive to PPD (3.2%) were found during chart review. Twenty-three patients with doubtful reactions (?+) were excluded. Of the patients, 75.3% ( $n = 149$ ) were female, and the mean age was 48.6 years (12–82 years). The grades of PPD patch test reactions in the cohort were recorded as 1+ for 56.6%, 2+ for 31.3%, 3+ for 7.1% when tested at 1.0% pet., and '4+' for 5.1%. Of the patients allergic to PPD, 16.6% ( $n = 33$ ) showed cross-reactions with one or more associated allergens in our baseline series. Of all patients sensitive to PPD, 5.1% reacted to DY3, 8.1% to IPPD, and 5.6% to caine mix. Of all patients allergic to PPD, 39% ( $n = 78$ ) had a confirmed history of hair dye use. A summary of these findings is listed in Table 1.

### Cross-reactions with increasing response to PPD

An increasing number of cross-reactions was seen with increasing reaction grade, whereby 16.1% with 1+ showed cross-reactions, 14.5% with 2+, 28.6% with 3+, and 50.0% with PPD (0.1–0.001%) ( $p = 0.02$ ; Cramér's  $V = 0.23$ ) (Fig. 1). When rates of cross-reactions per reaction strength were considered for each individual related allergen, we showed that, with DY3, there was a significant increase in cross-reactions per increase in reaction strength when 1+/2+ reactions were compared with 3+/4+ reactions ( $p = 0.04$ ). None of the other

**Table 1.** Summary of general findings

| Characteristics                                                      | Total n = 6130 |
|----------------------------------------------------------------------|----------------|
| Available records for patients with reactions to PPD, n (%)          | 221 (3.6)      |
| Patients sensitive to PPD (1–4+), which excludes 7+ reactions, n (%) | 198 (3.2)      |
|                                                                      | Total n = 198  |
| Female, n (%)                                                        | 149 (75.3)     |
| Median age in years (range)                                          | 48.6 (12–82)   |
| Reaction strength, n (%)                                             |                |
| +                                                                    | 112 (56.6)     |
| ++                                                                   | 62 (31.3)      |
| +++                                                                  | 14 (7.1)       |
| ++++                                                                 | 10 (5.1)       |
| Allergens related to PPD that showed cross-reactions, n (%)          |                |
| DY3                                                                  | 10 (5.1)       |
| IPPD                                                                 | 16 (8.1)       |
| Caine mix                                                            | 11 (5.6)       |

DY3, Disperse Yellow 3; IPPD, *N*-isopropyl-*N'*-phenyl-*p*-phenylenediamine; PPD, *p*-phenylenediamine. Reaction strength: as per International Contact Dermatitis Research Group criteria, as discussed in Materials and Methods.

n = number of patients.

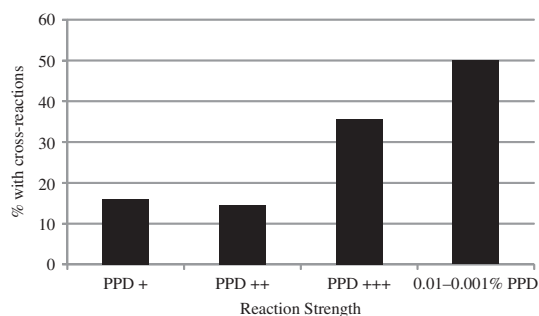


**Fig. 1.** Positive relationship of cross-reactions with increasing allergy response to *p*-phenylenediamine (PPD) ( $p = 0.02$ ; Cramér's  $V = 0.23$ ).

related allergens studied showed a significant relationship with reaction grade strength (Table 2).

It is of note that a history of hair dye use was positively related to an increasing ICDRG reaction grade ( $p = 0.01$ ; Cramér's  $V = 0.23$ ). When hair dye use in patients showing cross-reactivity was compared with reaction strength, a positive trend was noted ( $p = 0.28$ ).

## Discussion

The frequency of PPD allergy seen in the patch test population that we studied (3.2%) is consistent with those documented at our clinic in the 1980s and 1990s, although slightly lower than the 7.1% rate described in 2006 (7). In 2008, Schnuch et al. showed

**Table 2.** Comparison of grade of reaction to *p*-phenylenediamine (PPD) and cross-reactions with related allergens

|           | PPD reaction strength |      |                  |      | <i>p</i> |
|-----------|-----------------------|------|------------------|------|----------|
|           | +/++, n = 25          |      | +++ /++++, n = 8 |      |          |
|           | n                     | %    | n                | %    |          |
| DY3       | 5                     | 20.0 | 5                | 62.5 | 0.04     |
| IPPD      | 13                    | 52.0 | 3                | 37.5 | 0.38     |
| Caine mix | 9                     | 36.0 | 1                | 12.5 | 0.21     |

DY3, Disperse Yellow 3; IPPD, *N*-isopropyl-*N'*-phenyl-*p*-phenylenediamine; PPD, *p*-phenylenediamine. Reaction strength: as per International Contact Dermatitis Research Group criteria, as discussed in Materials and Methods.

n = number of patients who had cross-reactions.

sensitivity to PPD to be in the range of 3.6–4.2%. Our female/male ratio was 3:1, which is slightly higher than previously found by our own and other European centres (7, 13).

When assessing the rates of cross-reactions with related allergens, we found that 8.1% and 5.6% of patients also reacted to IPPD and caine mix, respectively. These rates are lower than those previously described in other centres. IPPD has been shown to cross-react in ~30% of cases (14, 15), and the rate of caine mix cross-reactions has been found to be ~2% (11), but also as high as 10% (7). It is of note that cross-reactions with caine mix are most commonly attributable to benzocaine, and seldom to dibucaine and tetracaine (16). The significance of the lower rates of cross-reactions with the above allergens seen in our data is not clear. The rate of cross-reactions with PPD and related allergens may actually be lower than previously thought.

This study shows that concomitant reactions to various allergens are common, which is in agreement with previous studies (7). Approximately 17% of our patients sensitive to PPD showed cross-reactions with one or more allergens. It is of interest that we showed an increasing rate of cross-reactions per reaction grade strength. A strong response (3+) to PPD 1% or any response to PPD 0.1–0.001% was associated with an approximately 50% chance of cross-reacting with other substances. This was previously shown by our group in Ho et al, where cross-sensitivity to caine mix showed a similar trend. This was also shown with another aromatic amine, Disperse Orange 3, by Goon et al in 2003. In our study group, we have shown that people are more likely to cross-react with Disperse Yellow 3 if they have stronger (i.e. 3+/4+) reactions to PPD ( $p = 0.04$ ). We were unable to show any significant relationship between cross-reactions with other individual allergens studied and increasing severity of PPD reaction. With the data collected, the

clinical relevance of the cross-reaction correlation was not evaluated. This is an interesting area of clinical relevance, and will require further study.

It has been previously shown that patients with a history of hair dye use have stronger responses to PPD (7, 17). This is in agreement with the observations in this study. We have also shown a significant increase in the number of cross-reactions per reaction grade strength in those who have a history of hair dye use (current or past).

At present, the significance of these relationships is unknown. Nevertheless, some groups advise their patients to avoid these related allergens, to prevent allergic responses. LaBerge et al. advise counselling patients who have positive reactions to PPD to avoid synthetic fibres such as nylon, polyester, and acetate, in case they contain textile dyes that are known to cross-react with PPD, notably Disperse Orange 3 (14.2%) (3). In our group, we currently do not advise patients to avoid these allergens.

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