

Severe allergic reactions to para-phenylenediamine in children and adolescents: should the patch test concentration of PPD be changed?

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Summary

Background: Semipermanent henna tattoos containing para-phenylenediamine (PPD) are a well-known cause of severe contact dermatitis, mainly in children. Another relevant exposure source to PPD are hair dyes, which are increasingly used by children and have also been reported to cause intense facial and scalp dermatitis. German patch test guidelines for children recommend that PPD should only be tested in patients who have had a henna tattoo, and then at a reduced concentration of PPD 0.5 % for 24 hours.

Patients and methods: We report on patch test results in four patients, three children and one adolescent, with a history of contact dermatitis to henna tattoos or hair dye. We used the recommended or even lower patch test concentrations of PPD with 24-hours exposure in all patients.

Results and conclusion: All patients showed very strong patch test reactions to PPD and cross-reactions to related compounds even after dilution of PPD to as low as 0.05 %. Therefore, we suggest that in children with a history of allergic reactions to this compound, a titration test should be performed beginning at a concentration of maximal 0.05 %. This procedure has also been proposed previously based on a larger cases series in adults.

Introduction

Semi-permanent henna tattoos, which are commonly obtained in tourist areas, continue to be popular among children. They are also known to result in severe contact allergies. Henna is often mixed with a synthetic dye known as para-phenylenediamine (PPD), sometimes in large concentrations, in order to achieve a long-lasting effect [1]. Numerous reports have shown that application of dark hair dyes, especially if done at home, can lead to sometimes severe contact dermatitis affecting the faces and scalp, the frequency of which tends to be underestimated [2]. For children and adolescents, this is another relevant exposure to PPD and related substances. Clinical experience has shown that following what is usually an extreme allergic reaction to PPD or related substances, the allergen should be tested

with caution, especially in children. Still, many patch tests continue to use the same concentrations for pediatric and adult testing [3]. International studies suggest using a test concentration of PPD 1 % in children. In Germany, there is concern about the sensitization potential even at this concentration [4] and therefore since 2005 PPD 1 % has not been included in the standard series of the German Contact Dermatitis Group (DKG). For patch testing in children up to 12 years of age, the DKG recommends limiting exposure to 24 hours and furthermore that PPD only be tested (at a concentration of 0.5 %) in those patients who have had a henna tattoo [5]. In the following case series, consisting of three children and one adolescent with contact allergies to semipermanent henna tattoos and hair dye, we report our experience with PPD

testing which demonstrate the need for using much lower test concentrations in children with the relevant history.

Patient 1

We describe a 17-year-old girl who began dying her hair at age 12 and who had a severe reaction, with edema and blistering on the face and scalp, two days after first using a permanent dye. Three months earlier she had gotten a henna tattoo while on vacation which has followed by contact dermatitis at the site of the tattoo. Due to the severity of the reaction, the girl was referred by her pediatrician to the pediatric unit of the University Hospital of Dresden and was treated in consultation with the dermatology unit. Two months after the condition healed, a patch test was performed with 24-hour exposure to the allergens.

Table 1: Positive patch test reactions to DKG standard and hairdresser's series.

	24 hrs.	48 hrs.	72 hrs.
PPD 0.5 %	+++	+++	+++
p-toluylendiamine 0.5 %	+++	+++	+++
p-aminophenol 0.5 %	neg.	++	++
3-aminophenol 1 %	++	++	++
Benzocaine 5 %	+++	++	++
N-isopropyl-N-phenyl-p-phenyldiamine 0.1 %	++	++	++
Hydroquinone 1 %	neg.	++	++
Pyrogallol 1 %	++	++	++
Dispersion mix blue 124/106 1 %	?	++	++
Thiuram mix 1 %	?	+	+
Mercapto mix without MBT 1 %	?	++	+
Fragrance mix 8 %	?	?	+
Propolis 10 %	neg.	+	+

The results showed a highly positive reaction to PPD, p-toluylendiamine, and p-aminophenol despite dilution of the test substances to 1 : 1 (e.g., PPD 0.5 %). Exposure to PPD resulted in a bullous reaction. There were also numerous cross-sensitizations, e.g., to 3-amino phenol, benzocaine, and azo dyes (dispersion mix blue). Due to the mainly cross-reactive test reactions, "angry back" was largely excluded (Table 1, Figure 1).

**Figure 1:** Bullous reaction to PPD 0.5 % (pet.) at 24 hrs.**Figure 2:** Simultaneous contact dermatitis to a henna tattoo in two brothers.

Patients 2 and 3

The brothers M. (7 years old) and K. (5 years old) simultaneously developed contact dermatitis in henna tattoos which they had received at the same time in Hungary. Within a week of painting of the tattoo, the first inflammatory skin reaction had appeared at the tattoo site on the right upper arm. The rash then spread quickly to the extremities and trunk. After returning from vacation (after a total of 3 weeks) both children were brought to the emergency dermatology unit of our hospital. There was a severe skin reaction with vesicles and inflammation in the tattoos (Figure 2) with

spread of a papulovesicular rash to the flanks (M.) as well as the hands and feet (K.). Despite topical corticosteroids (prednicarbate), the reaction continued to spread, necessitating hospitalization in our hospital's pediatric unit. M. was given a 6-day regimen of prednisolone, starting with 20 mg followed by topical therapy with betamethasone valerate and fusidic acid.

A patch test was performed six weeks after clearance of the lesions. The PPD concentration was diluted to 0.1 % (24-hour exposure). Both brothers developed an exudative, +++ positive reaction (Table 2, Figure 3) with a nearly identical spectrum of cross-sensitization.

Patient 4

N., 4 years old: one-and-a-half weeks after getting a henna tattoo while on vacation in Turkey, an exudative inflammation appeared in the tattoo and there were isolated lesions in the surrounding area.

Three weeks after the tattoo was painted, the girl was brought to the emergency dermatology unit of our hospital with a papulovesicular inflammation in the tattoo on the right forearm and individual lesions on the right hand. The patient was otherwise in good health. Treatment was begun with topical prednicarbate cream.

A week later, the father brought the girl to the hospital again. She now had a systemic reaction with dermatitis and erythema multiforme-like lesions on the face (Figure 4) and on the backs of the hands (Figure 5). The earlobes had

Table 2: Positive reactions in a simultaneous patch test performed in two brothers.

72 hr. reading	M.	K.
PPD ca. 0.1 %	+++	+++
p-toluylendiamine	+++	+++
p-aminophenol	+++	+
Dispers. orange	+++	+++
Dispers. yellow	++	+
Dispers. red	+	neg.
Acid yellow 36	+	+
Bismark Brown R	+	+
Standard pediatric: thiuram mix	+	+
Standard pediatric: fragrance mix	++	neg.

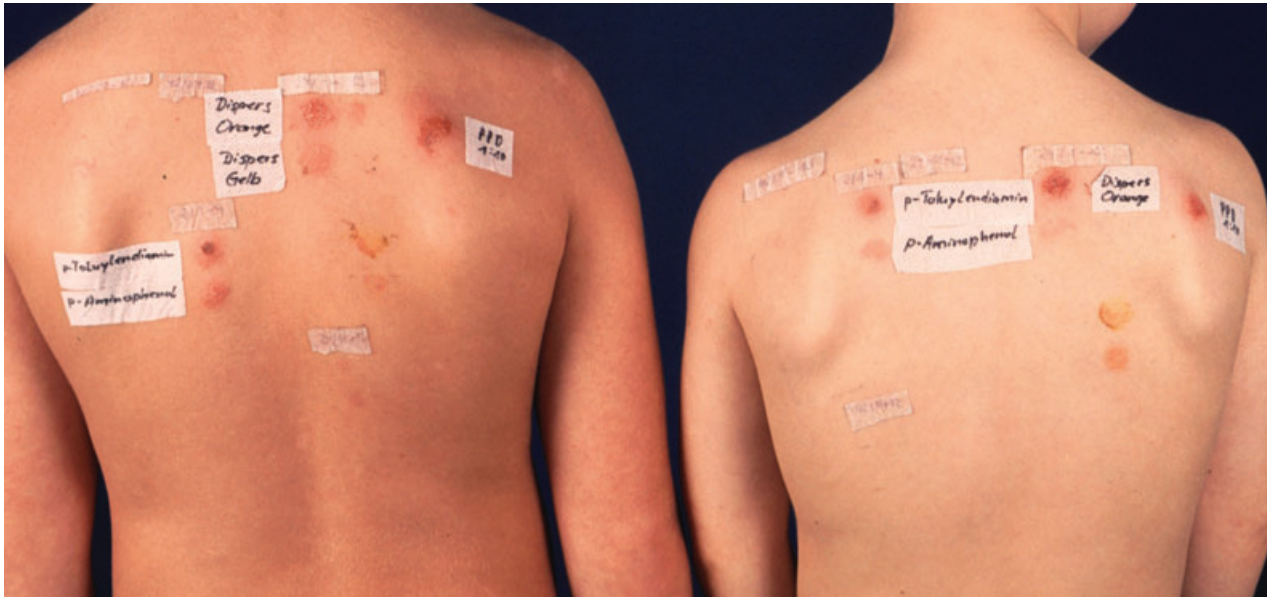


Figure 3: Simultaneous patch test in two brothers, PPD 0.1 % (pet.) at 24 h.



Figure 4: Dermatitis – and erythema multiforme like patches on both cheeks.



Figure 5: Erythema multiforme-like patches on the back of hands.



Figure 6: Pseudolymphoma-like appearance on the earlobes.

a pseudolymphoma-like appearance (Figure 6). Systemic corticosteroid therapy was rejected and thus topical therapy was continued until the lesions healed.

A patch test was performed three months later including PPD 0.05% (24-hour exposure) which resulted in a +++ positive, but still acceptable reaction. There was also cross-reactivity, mainly with azo dyes (Table 3, Figure 7).

Comments

The case reports described here clearly demonstrate that for testing of paraphenyldiamine, even if the current recommendations for pediatric patients (concentration of 0.5 % and 24-hour exposure) are followed, strong test reactions can occur. It should be emphasized that the main source of exposure to PPD in children is semipermanent henna tattoos containing PPD which is supposed to make the tattoo darker. While the bro-

wish extract from the henna plant (*Lawsonea inermis*) has minimal sensitization potential, PPD is a highly potent allergen. PPD is a precursor of azo dyes, which often cause cross reactions with other dyes in the same group as well as with substances in rubber and local anesthetics. In one human maximization test, all test subjects ($n = 24$) were sensitized after exposure to 10 % PPD [6]. PPD is usually found in henna preparations in concentrations of about 6 % [7],

although one study reported a maximum concentration of 15.7 % [1]. Thus in children, under certain circumstances it may be advisable to assume the presence of sensitization. The simultaneous development of contact dermatitis in both of the brothers described here also supports this. All of the patients described in the above had received henna tattoos and were thus presumably sensitized to PPD. The intensity of sensitization is determined by the potency of the allergen as well as its induction dose [8]. These factors,

Table 3: Patch test result in N., 4 years old.

	24 hrs.	48 hrs.	72 hrs.
PPD ca. 0.05 %	+	+++	+++
Dispers. orange 3. 1 %	++	+++	+++
Dispers. yellow 3. 1 %	neg.	+	?
Dispers. red 1. 11. 17. 1 %	neg.	neg.	17 questionably pos.
Dispers. blue 3. 106. 124. 1 %	neg.	neg.	neg.
Acid yellow 36. 1 %	neg.	+++	+++
4-amino benzoic acid (PABA). 1 %	neg.	neg.	neg.
Lidocaine HCL 15 %	neg.	neg.	neg.
Procaine HCL 2 %	neg.	neg.	neg.
Benzocaine 5 %	neg.	neg.	neg.

**Figure 7:** Patch test result with PPD 0.05 % (pet.) at 24 hrs.

along with the presence of the allergen on the skin for an extended period of time, are probably the main explanation for the extreme reaction to PPD as well as to subsequent patch tests.

While a number of case reports [9–11] have indicated the importance of henna tattoos in severe contact dermatitis in children, the etiological role of hair dyes containing PPD or related substances such as para-toluyldiamine is less certain. Hair dyes are another main source of exposure to these substances in children and adolescents, as interview-based studies done in Denmark have shown: In

these studies, the age at which children first dyed their hair was 16 years [12]. A current study reported even younger ages (13.3 years), and for those in training to be hairdressers the age was even lower at 12.1 years [13]. In an earlier study by this working group, 55 cases of severe scalp dermatitis after the use of hair dye were reported in adults. Only 29 % sought the advice of a dermatologist or underwent testing, and thus one can assume a significant amount of underreporting [2]. Additional allergen sources for sensitization to PPD were not queried in the study.

In a recent analysis of the data of from the Information Network of Departments of Dermatology (IVDK) in Germany, occupational and non-occupational exposure to hair dye contributed equally to the majority of identifiable causes of contact allergy to PPD. The test reactions to PPD for dermatitis affecting the face and scalp were significantly stronger than for dermatitis affecting other sites [14]. In addition, PPD was the most common cause of contact dermatitis of the face and scalp which also suggests the clinical relevance of hair dye [15].

Yet there are also signs that sensitization to hair dyes often also occurs as a result of a henna tattoo, as occurred in our first patient. In addition to similar case studies [16, 17], a recent analysis of the side effects associated with hair dyes (reported to manufacturers) showed that having had a henna tattoo is a main risk factor for the severity of an allergic reaction to a hair dye [18]. Thus in patients with a history of contact dermatitis of the scalp due to hair dye, a strong patch test reaction to PPD and related substances should also be expected.

Several large studies exist from various countries on the frequency of positive patch test reactions to PPD. These studies also address the sensitization spectrum among children. The prevalence of sensitization to PPD among children who were brought for patch testing (i.e., not the general population) is about 2 % in children up to 12 years of age [19] and between 2 and 4 % if adolescents are included [20–22]. This roughly corresponds to the frequency among adults. Based on data from the IVDK, the prevalence of positive reactions to PPD was 4 % (or 1 % if these results are extrapolated to the total general population) [14]. In Great Britain and Turkey, pediatric sensitization rates to PPD are up to 9 % [23, 24]. Yet the results of international studies are difficult to compare given potentially different referral criteria and different typical exposures. Even if the prevalence of positive reactions to PPD in children does not differ significantly from that in adults (because the majority of tested children are not sensitized), with targeted testing, i.e., given the relevant patient history, a higher rate of positive reactions and stronger reactions may be assumed.

Systematic analyses on the severity of reactions to patch testing with PPD are still largely lacking. In one study from Great Britain, a history of reactions to hair dye was shown to be related to a more severe patch test reaction to PPD [25]. In a case series of 11 adults and one child who had previously had henna tattoos, the authors discussed the issue of an unacceptably strong patch test reaction to PPD 1 % and thus recommended beginning with 0.01 % [26].

Based on the case series presented here, an age-stratified analysis of the IVDK data on the reaction severity to PPD was performed and the results were subsequently published. These showed that children up to 14 years of age (i.e., without occupational exposure) had a significantly higher proportion of +++ reactions to PPD compared with all other age groups. For nickel sulfate, fragrance mix, and methyl-(chloro-) isothiazolinone (MI/MCI) as a substance with similar allergenic potential to PPD, a similar effect was not seen [27]. This suggests that children do not exhibit altered patch test reactivity per se, but rather that there is increased sensitization to PPD due to prior exposure. The majority of children with a +++ reaction had a history of exposure including henna tattoos or hair dyes. In this study as well, in children with the respective history, testing began with concentrations of 0.01 %.

To summarize, we conclude that based on the clinical appearance and current studies the standard concentrations of PPD 1 % and even 0.5 % may be far too high for pediatric use in children with a history of exposure related to henna tattoos or to hair dyes. This is especially true for children who previously had an allergic reaction to these sources. Yet if there is no such history, then there is hardly a reason, according to the DKG, to test these substances in children, and hence dilution may be assumed to be necessary in those patients who do need testing. The same applies to adolescents over 12 years of age who have had non-occupational exposure to PPD and who have a relevant patient history. Adolescents are often tested, like adults, with PPD 1 %. Given that there is no commercial preparation available for test concentrations below 1 %, it is not inconceivable that in some situations, where there is a clear clinical relationship and a risk of a severe reaction, PPD may

not even be tested. Yet we would suggest, for patch testing with PPD in children and adolescents with a history of allergic reactions to henna tattoos or hair dyes, that testing begin with 0.05 % or less, with 10-fold increases to a maximum of 1 % or 0.5 % in children under age 12. The often numerous cross-sensitizations should also be tested as these may later limit career options. Allergic reactions to PPD in children and adolescents should be documented as thoroughly as possible, especially due to the increasing use of dark hair dyes in this age group. <<<

Conflict of interest

None.

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