



Contents lists available at ScienceDirect



Occupational asthma, rhinitis, and contact urticaria caused by oxidative hair dyes in hairdressers

Eva Helaskoski, MD^{*,§}; Hille Suojalehto, MD[†]; Hannele Virtanen, MD, PhD[‡]; Liisa Airaksinen, MD, PhD[‡]; Outi Kuuliala, MSc[†]; Kristiina Aalto-Korte, MD, PhD[‡]; and Maria Pesonen, MD, PhD[†]

^{*} Department of Occupational Medicine, Finnish Institute of Occupational Health, Helsinki, Finland

[†] Control of Hypersensitivity Diseases, Finnish Institute of Occupational Health, Helsinki, Finland

[‡] Skin and Allergy Hospital, Helsinki University Hospital, Helsinki, Finland

[§] Department of Public Health, Hjelt Institute, University of Helsinki, Helsinki, Finland

ARTICLE INFO

Article history:

Received for publication May 21, 2013.

Received in revised form August 29, 2013.

Accepted for publication October 3, 2013.

ABSTRACT

Background: Oxidative hair dyes commonly contain paraphenylenediamine (PPD) and its derivatives, a well-known cause of delayed hypersensitivity among both consumers and hairdressers. They are also considered possible causes of occupational respiratory diseases. Despite the widespread use of hair dyes, there are only a few reports of asthma, rhinitis, and contact urticaria caused by PPD and related compounds. **Objective:** To characterize patients with occupational asthma, rhinitis, or contact urticaria associated with oxidative hair dyes and to evaluate the diagnostic methods.

Methods: We reviewed the patient files of the Finnish Institute of Occupational Health for the period January 1, 2001, through May 31, 2011, to identify patients diagnosed as having asthma, rhinitis, or contact urticaria associated with oxidative hair dyes. The diagnoses of asthma and rhinitis were based on specific inhalation challenges with hair dye products. Skin prick tests were performed with hair dye ingredients as hapten conjugates of human serum albumin and with hair dye products and ingredients as is. Open skin tests confirmed the diagnosis of contact urticaria.

Results: We describe 11 hairdressers with occupational asthma (5 cases), rhinitis (5 cases), and contact urticaria (3 cases) due to hair dyes. Of the 52 specific inhalation challenges performed, 9 (17%) had positive results. One patient who experienced an anaphylactic reaction when having her own hair dyed had positive skin prick test results to PPD and toluene-2,5-diamine sulfate.

Conclusion: Hairdressers are at risk for occupational asthma, rhinitis, and contact urticaria due to oxidative hair dyes. Skin prick testing may be insensitive for detecting immediate hypersensitivity to PPD and related compounds.

© 2013 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Respiratory symptoms and contact dermatitis are frequent concerns among hairdressers.^{1–3} Hairdressers are at an increased risk of occupational hand eczema due to frequent contact with the skin irritants and contact allergens in hairdressing chemicals.⁴ They are also exposed to several airborne irritating factors^{5,6} and allergens in their work, such as the persulfate salts in hair bleaching products, which are a major known cause of occupational asthma (OA) and occupational rhinitis (OR) among hairdressers.^{7–12}

Paraphenylenediamine (PPD), an organic aromatic amine, is a common ingredient of oxidative hair dyes.¹³ PPD and its derivatives are known as potent skin sensitizers,¹⁴ and positive patch test reactions to PPD are frequent among patients with dermatitis.^{15–17} The predominant cause of delayed contact allergy to PPD is exposure

to oxidative hair dyes.¹⁸ Delayed contact allergy to PPD and related para-amino compounds, such as toluene-2,5-diamine sulfate (TDS), are a well-known cause of allergic contact dermatitis in both hairdressers and consumers who dye their hair.¹⁹ Hairdressers and beauticians are at an increased risk of delayed PPD sensitization,²⁰ and the reported prevalences of PPD sensitization among hairdressers with dermatitis have been high (24% to 54%).^{21,22} Several studies have reported an increasing frequency of delayed PPD sensitization,^{16,23} most probably resulting from the increased use of hair dyes.²⁴

Previously, only a few cases of immediate hypersensitivity to PPD have been reported in the literature.^{25–28} Anaphylaxis associated with exposure to hair dyes that contain PPD or related compounds may occur,^{29–31} and even one fatal case of anaphylaxis from hair dye use has been reported.³² Airborne exposure to PPD has been associated with respiratory symptoms.^{33,34} However, few previous reports exist on OA and OR due to PPD.^{9,35,36}

The aim of the present study was to characterize patient cases of occupational immediate-type skin and respiratory diseases

Reprints: Eva Helaskoski, MD, Finnish Institute of Occupational Health, Topeliuksenkatu 41 a A, FI-00250 Helsinki, Finland; E-mail: eva.helaskoski@ttl.fi.

Disclosures: Authors have nothing to disclose.

associated with oxidative hair dye exposure. We describe 11 cases of hairdressers diagnosed as having immediate-type reactions (ie, OA, OR, and occupational contact urticaria [OCU]) caused by hair dyes containing PPD-related para-amino compounds and the diagnostic methods used. One of the patients experienced an anaphylactic reaction when having her own hair dyed with an oxidative hair dye that contained TDS.

Methods

Study Participants

The occupational medicine clinic at the Finnish Institute of Occupational Health receives patients with suspected occupational disease from all over Finland, which has a population of approximately 5.4 million. Work-related respiratory and dermatologic symptoms are the most common indications for referral to the clinic. The routine examinations of hairdressers referred to the clinic for immediate-type work-related symptoms include skin prick tests (SPTs) with common environmental allergens and the most common hairdressing chemicals. In case of respiratory symptoms, lung function tests (spirometry and histamine challenge) and exhaled nitric oxide measurement are performed, and serial peak flow monitoring at work and off work is included whenever feasible. Specific challenge tests (inhalation and skin) are used to confirm the diagnosis. We retrospectively reviewed the medical files of patients with a suspected occupational disease for the period of January 1, 2001, through May 31, 2011, to identify patients diagnosed as having OCU, OR, or OA associated with oxidative hair dyes. We also reviewed the files for SPTs and specific inhalation challenges (SICs) performed with oxidative hair dyes at the clinic during the same period. From the medical records, we collected data on the patients' occupational history, exposure to hair dye products, type of symptoms related to work (cutaneous, bronchial, and nasal), the association between symptoms and specific substances or work tasks, the duration of exposure before the onset of symptoms, the duration of symptoms before diagnosis, and the history of atopy and smoking. We also examined the results of the clinical examinations, immunologic tests, and SICs.

SPTs and Measurement of Serum IgE

SPTs with common environmental allergens were performed with standardized allergen extracts of birch, alder, timothy grass, meadow fescue, mugwort, cat, dog, horse, cow, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria alternata*, *Cladosporium herbarum* (ALK, Copenhagen, Denmark), and natural rubber latex (Stallergenes SA, Antony, France). These tests included histamine hydrochloride (10 mg/mL) and a diluent control.

SPTs with PPD and TDS were performed with hapten conjugates of human serum albumin (HSA) prepared according to the method of Howe et al.³⁷ Three of the patients also underwent SPTs with hair dye products and hair dye ingredients as is and as various dilutions in aqua and ethanol. A positive SPT reaction was defined as a wheal with a mean diameter of at least 3 mm and equal to or greater than half of the diameter of the histamine wheal.

Serum total IgE was measured using the Phadia UniCAP System (Phadia, Uppsala, Sweden). A total IgE level less than 110 kU/L was regarded as normal.

Open Skin Testing

An open skin test (ie, an open application test) was performed to confirm the diagnosis of contact urticaria due to oxidative hair dye. We tested the hair dye products both as is and with the oxidant (ie, hydrogen peroxide). The test substance was applied thinly on a 5 × 5-cm area of healthy skin on the forearm. The test area was inspected at 20 minutes, and if the result was negative, the

application was repeated in the same area for another 20 minutes. The test area was then reinspected and the test material removed. All the open skin test results were read and interpreted by a dermatologist. A positive open skin test reaction was defined as one or several urticarial wheals appearing on the test area.

Patch Testing

Only the patients with a history of eczema underwent patch testing, for which we used the Finn Chamber method (Epitest, Tuusula, Finland) according to the recommendations of the International Contact Dermatitis Research Group. The tests were read 2 or 3 times, depending on the day of the week on which the test patches were applied. PPD and TDS were patch tested as 1% in petrolatum with commercially available test substances (Trolab; Almirall Hermal GmbH, Reinbek, Germany).

Lung Function Tests and Fractional Exhaled Nitric Oxide

We performed the flow-volume spirometry and bronchodilation tests in accordance with the American Thoracic Society criteria,³⁸ using a standard spirometer (Spirostar USB; Medikro, Kuopio, Finland) and the predicted values for the Finnish population. We performed the bronchial challenge with histamine according to the method described previously.³⁹ We measured the provocative dose causing a 15% reduction in forced expiratory volume in 1 second (FEV₁) (PD₁₅). Bronchial hyperresponsiveness was graded as follows: severe, PD₁₅ less than 0.1 mg; moderate, PD₁₅ of 0.1 to 0.4 mg; mild, PD₁₅ of 0.4 to 1.6 mg; and no hyperresponsiveness, PD₁₅ greater than 1.6 mg. Serial peak expiratory flow measurements during days at work and days off were performed according to the method of Burge.⁴⁰ We measured exhaled nitric oxide using an online chemiluminescence analyzer (NIOX; Aerocrine AB, Solna, Sweden) and interpreted it according to current recommendations.^{41,42}

Specific Inhalation Challenge Tests

Patients with suspected OA or OR underwent SICs in a 6-m³ challenge chamber for 2 or 3 subsequent days, each with a 24-hour follow-up. In the control tests, lactose powder was puffed into the breathing zone from a bowl with pressured air in 1-minute intervals for 30 minutes. The SIC with oxidative hair dye was performed as a work simulation: the patient mixed a dose (60–80 mL) of oxidative hair dye with an oxidant that contained hydrogen peroxide (3%–12%) for 30 minutes. The hair dye product suspected to have caused the patient's respiratory symptoms was used. Six patients also underwent an SIC with a hair bleach product that contained persulfates and an oxidant that contained hydrogen peroxide.

The test result was considered positive for OA when there was a sustained decrease in FEV₁ of 20% or more from the prechallenge value, in the absence of significant ($\geq 10\%$) changes in the control test.⁴³ The positive bronchial reactions were classified into 3 patterns: early reactions occurred within an hour after the end of exposure, late reactions within 1 to 8 hours, and dual reactions consisted of both early and late reactions.

The degree of rhinorrhea and nasal blockage of patients with suspected OR was evaluated by anterior rhinoscopy before the SIC and approximately 20 minutes after the end of the SIC. Rhinorrhea and nasal blockage were scored on a range of 0 (dry or thin mucosa) to 3 points (dripping mucus or swelling of the mucosa). We also measured the amount of nasal secretion running out of the patient's nose and to the vestibulum of the nostrils. The results were interpreted according to the scoring system described by Hytonen et al.,⁴⁴ and OR was considered to be the case if the control SIC test result was negative and the score changed by 4 points or more in both nostrils in the SIC with a hair dye. Nasal secretion of

Table 1
Characteristics of the study patients

Patient No.	Sex	Age, y	Smoking	Duration of exposure before symptoms, y	Duration of symptoms before diagnosis, y	Total IgE, kU/L ^a	SPT common environmental allergens	FEV ₁ , predicted %	Degree of nonspecific hyperresponsiveness ^b	Exhaled nitric oxide ^c	Serial PEF measurements at work/off work
1	F	25	Yes	1	2	410	Negative	81	Mild	3.7	NT
2	F	32	No	10	2	44	Negative	90	Moderate	49.3	Negative
3	F	33	Ex	6	9	34	HDM	92	Mild	14.8	Positive
4	F	52	No	20	7	30	Negative	78	None	NT	NT
5	F	21	No	4	1.5	101	Negative	91	None	4.9	Positive
6	F	42	No	20	2	6	Negative	118	None	18.6	Negative
7	F	27	No	5	3	53	Pollen, animal dander, HDM	98	Mild	NT	NT
8	M	41	Yes	12	10	2150	Pollen, animal dander	83	Severe	NT	NT
9	F	39	No	14	6	112	Pollen, animal dander	115	None	7.3	NT
10	F	29	No	7	3	355	Pollen, animal dander, HDM	115	None	55.4	Negative
11	F	34	Yes	2	12	682	Negative	83	None	NT	Negative

Abbreviations: FEV₁, forced expiratory volume in 1 second; HDM, house dust mite; NT, not tested; PEF, peak expiratory flow; SPT, skin prick test.

^aTotal IgE less than 110 kU/L regarded as normal.

^bMeasured with histamine challenge.

^cExhaled nitric oxide less than 50 ppb indicates that eosinophilic inflammation is likely.

more than 200 mg supported the scoring positivity.⁴⁵ Acoustic rhinometry was performed before and after the challenge.

Ethical Considerations

The patient file and database review was approved by the ethical board of the Finnish Institute of Occupational Health (approval TTL/1/2008). According to local legislation, ethical committee approval was not needed because no patient intervention was applied.

Results

SPTs and Specific Inhalation Challenge Tests With PPD and Oxidative Hair Dyes

SPTs with PPD-HSA conjugate were performed 166 times during the study period. The SPTs were mainly performed on hairdressers who had handled hair dye products containing PPD and related para-amino compounds and who had experienced possible allergic symptoms in their work. Of the 166 SPTs with PPD-HSA conjugate, only 1 was positive (patient 1). SICs with oxidative hair dye products were performed on 52 patients with suspected OR and/or OA. Of these, 5 (9.6%) had a positive bronchial and 5 (9.6%) a positive nasal reaction to the hair dye product. The patients with negative SIC results to oxidative hair dye also underwent SICs with other possible causative agents, such as persulfates and permanent wave solutions.

Patients With Occupational Immediate-Type Skin and Respiratory Diseases Caused by Oxidative Hair Dyes

We identified 11 patients diagnosed as having occupational immediate-type skin and respiratory diseases due to oxidative hair dye, all of them hairdressers. Table 1 presents the characteristics of the patients. Ten were female. The mean age at the time of diagnosis was 34 years (range, 21–52 years). The mean exposure time before the work-related symptoms appeared was 9 years (median, 7 years). The mean duration of the symptoms before the occupational disease diagnosis was 4.5 years (median, 3 years). Five of the patients had one or several positive reactions to common environmental allergens. Of the 11 patients, 3 were diagnosed as having OCU caused by oxidative hair dyes, 5 as having OA, 5 as having OR, and 2 as having concomitant allergic contact dermatitis (Table 2).

Medical History and Diagnostic Tests in Patients With Contact Urticaria to Oxidative Hair Dyes

Three of the 11 patients (patients 1–3, Table 2) reported symptoms suggestive of contact urticaria caused by oxidative hair dyes and were examined with open skin testing with the hair dye products. Patient 1 had hand eczema and recurrent rash on the scalp, face, and neck after dyeing her own hair. She also reported urticaria that appeared immediately on her hand where oxidative eyelash dye that contained TDS and 2-chloro-p-phenylenediamine had been spilled. When having her own hair dyed with an oxidative hair dye that contained TDS, she developed anaphylaxis (nausea, abdominal pain, difficulty in breathing, widespread urticaria, and edema) within 10 minutes of the dye application. The SPTs on patient 1 resulted in a 6-mm wheal to histamine and 4-mm wheals to PPD-HSA and TDS-HSA conjugates, which were reproducible in repeated testing. Black hair dye as is, eyelash dye as is, and the oxidant of the hair dye product were SPT negative. We obtained the ingredients of the black hair dye from the manufacturer and performed SPTs with 0.01% to 1% dilutions. Of the 16 ingredients, only TDS (tested as a HSA conjugate) was SPT positive. In open skin testing, the hair dye associated with anaphylaxis and the eyelash dye associated with contact urticaria were mixed with the oxidant for testing. Both of the dye-oxidant mixtures produced urticarial wheals on the test area. The result of the hair dye tested as is without the oxidant was negative. Patient 1 had also experienced work-related cough and dyspnea. She was diagnosed as having asthma based on diurnal variation in serial peak expiratory flow measurements. Because of the history of anaphylaxis, an SIC with a hair dye was not performed. Therefore, we could not establish an association between the patient's work-related respiratory symptoms and oxidative hair dyes.

Patients 2 and 3 were SPT negative to PPD-HSA conjugate but had a positive reaction to oxidative hair dye products in open skin testing. Patient 3 was also SPT negative to a total of 12 oxidative hair dye products from the patient's workplace. Open skin tests with 5 different oxidative hair dyes as is all produced strong edema and erythema that spanned the whole test area. Urticarial wheals appeared on one of the hair dyes' test areas. The 23 ingredients of this hair dye product were obtained from the manufacturer and SPT and open skin tested, with negative results. Surprisingly, the result of a repeated open skin test with the same hair dye product that had previously produced urticarial wheals was negative. It turned out that the patient had taken 400 mg of ibuprofen for headache the night before the test. Open skin test with the hair dye was later

Table 2

Patients with occupational disease due to oxidative hair dye products

Patient	Occupational disease due to oxidative hair dyes	SPT to PPD-HSA	SIC tests with oxidative hair dye mixed with oxidizing agent		Open skin test ^b	Patch test reactions to hair dye ingredients
			Bronchial reaction ^a	Nasal reaction		
1	Contact urticaria with anaphylaxis, allergic contact dermatitis	Positive, TDS-HSA positive	NT	NT	Oxidative hair dye containing TDS 10%: negative; hair dye containing TDS mixed with oxidant: positive; eyelash dye containing TDS mixed with oxidant: positive	PPD ++, TDS ?+, 4-aminoazobenzene ++
2	Contact urticaria	Negative	NT	NT	Hair dye containing TDS: 20% and 100%: positive	PPD, TDS, and all tested hair dye products neg.
3	Contact urticaria, asthma	Negative	Late, FEV ₁ –34%	Negative	Oxidative hair dyes (5 products) 100%: positive; probably nonimmunologic CU	PPD, TDS, and all tested hair dye products neg.
4	Asthma	NT	Early, FEV ₁ –22%	Negative	NT	NT
5	Asthma	Negative	Dual, FEV ₁ –21%	Negative	NT	NT
6	Asthma	NT	Early, FEV ₁ –22%	Negative	NT	NT
7	Asthma, rhinitis	NT	Early, FEV ₁ –28%	Positive; masal secretion, 1,100 mg	NT	NT
8	Rhinitis, allergic contact dermatitis	Negative	Negative	Positive; nasal secretion, 1,120 mg	NT	PPD ++, TDS ++, 2-nitro-4-phenylene diamine +++, 4-aminoazobenzene +++, own hair dye 5% +++
9	Rhinitis	Negative	Negative	Positive; masal secretion, 430 mg	NT	NT
10	Rhinitis	Negative	Negative	Positive; nasal secretion, 660 mg	NT	NT
11	Rhinitis	Negative	Negative	Positive; nasal secretion, 300 mg	NT	NT

Abbreviations: FEV₁, forced expiratory volume in 1 second; HSA, human serum albumin; NT, not tested; PPD, paraphenylene diamine; SIC, specific inhalation challenge; SPT, skin prick test; TDS, toluene-2,5-diamine sulphate.

^aDescribed as reaction type and maximal percentage FEV₁ decrease.

^bOpen skin testing was performed only in patients with contact urticaria associated with hair dye.

repeated without previous nonsteroidal anti-inflammatory medication, and the result was again positive. The hair dye product was open skin tested on 2 control patients, and caused edema and erythema that spanned the whole test area of both patients. The test results were interpreted as indicating nonimmunologic contact urticaria caused by the hair dye.

Diagnostic Tests in Patients With Occupational Respiratory Diseases

The diagnosis of OA and/or OR were based on SIC results. Nine patients (patients 3–11) had positive SIC reactions to an oxidative hair dye product they had been using at work (Table 2 and Fig 1). One of them (patient 7) had both OA and OR. Six of the 9 patients also underwent a 30-minute SIC with a bleaching product that contained persulfates (3%–12%) and oxidants, with negative results.

Five of the patients used inhaled corticosteroid medication when entering the examinations. Baseline FEV₁ was normal in all except 1 patient, who had mild obstruction. In 3 patients, we detected nonspecific hyperresponsiveness before the SIC. We performed serial peak expiratory flow measurements at work and on days off in 5 of these 9 patients. Three of them were subsequently diagnosed as having OA due to hair dyes, and for 2 of them the serial peak expiratory flow measurements at work and on days off were compatible with OA. Positive bronchial reactions were classified as early in 3 patients, as dual in 1 patient, and as late in 1 patient (Table 2 and Fig 1).

In all 5 OR cases, the control SIC test results were nonsignificant, and marked rhinorrhea appeared after the SIC with a hair dye (positive scoring and nasal secretion of 300–1,120 mg). The diagnosis of OR was based on watery rhinorrhea and a score change of

4 points or more in accordance with the scoring system used. Acoustic rhinometry measurements revealed unspecific changes only.

Discussion

In the present study, we examined the medical records of 11 hairdressers diagnosed as having OA, OR, or OCU caused by oxidative hair dyes that contained PPD or related para-amino compounds, such as TDS. In contrast to delayed allergy, type 1 hypersensitivity reactions to PPD and related compounds appear to be rare. Contact urticaria to oxidative hair dyes has been reported,^{25,26,34} as well as combined immediate and delayed hypersensitivity to PPD,^{27,28} as in the case of our patient 1. A few cases of anaphylaxis associated with hair dye have been reported,^{29,46} among them even a fatal case.³² OA and OR due to PPD exposure have been occasionally reported.^{9,35,36}

Only a few cases of positive results on SPT or scratch tests to PPD or related compounds have been previously reported.^{34,46,47} To our knowledge, the detection of specific IgE to PPD or to its derivatives used in oxidative hair dyes has not been described in the literature.

In our patient series, the result of a SPT with PPD-HSA conjugate was positive only in patient 1, who had experienced anaphylaxis associated with oxidative hair dye. Of the total 166 patients undergoing SPTs with PPD-HSA conjugate during the last 10 years in our clinic, this is the only SPT-positive case, which is in line with the general view that the sensitivity of SPTs with PPD and related compounds is low. Patient 1 was also SPT positive to TDS-HSA conjugate but not to PPD and TDS tested as such (ie, without HSA conjugation). Further studies are needed to clarify whether HSA conjugating improves SPT sensitivity in immediate allergy to

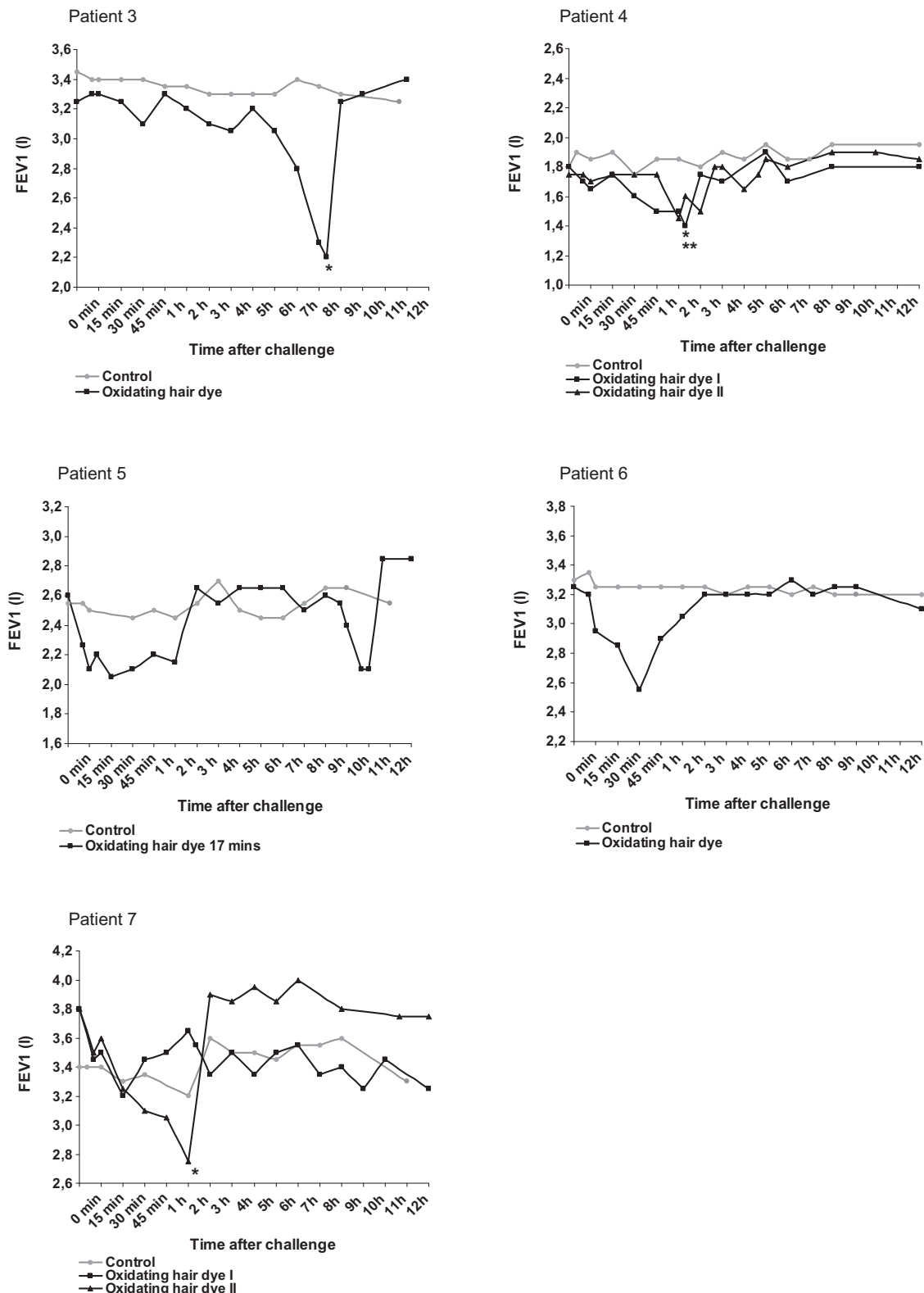


Figure 1. Results of specific inhalation challenges for 5 patients illustrating the changes in forced expiratory volume in 1 second (FEV₁) to control agent (lactose powder) and oxidating hair dye. The duration of the exposure was 30 minutes if not stated otherwise. In 2 patients (patients 4 and 7) inhalation challenge with oxidating hair dye was repeated. Asterisk indicates bronchodilator medication; double asterisk indicates prednisolone.

PPD and related compounds, such as TDS. So far, we have not tested the TDS-HSA conjugate in other patients.

Open skin test reactions to hair dyes in patients with negative SPT to PPD results may be due to nonimmunologic contact

urticaria. The open skin test reaction to hair dye of patient 2 was temporarily inhibited during nonsteroidal anti-inflammatory (ibuprofen) medication, which suggests a diagnosis of non-immunologic contact urticaria.⁴⁸

Our 11 patients diagnosed as having OA, OR, or OCU associated with occupational oxidative hair dye exposure were mainly young women, which reflects the general sex and age distribution of hairdressers. Occupational diseases due to oxidative hair dyes commonly coexisted in our patients: 4 of them had more than 1 of these diseases and 2 of them had simultaneous skin and respiratory diseases. In addition, patient 1, who had OCU and allergic contact dermatitis, may also have had OA to oxidative hair dyes, but no SIC was performed because of previous anaphylaxis. The simultaneous occurrence of OR and OA is common, but the coexistence of respiratory and skin disease has been less frequently reported.⁴⁹

In most of the patients, lung function and exhaled nitric oxide were normal or nearly normal and no hyperresponsiveness was detected. The fact that 5 patients were taking inhaled corticosteroid medication when they took part in the examinations may have affected these parameters. Serial peak expiratory flow recording at work and on days off was available in only 3 patients with OA caused by oxidative hair dyes. Two peak expiratory flow recordings were interpreted as being positive to OA, which supports the SIC findings.

In our patient material, of the 52 patients with suspected occupational respiratory disease tested by an SIC to oxidative hair dyes, 9.6% had a positive bronchial and 9.6% a positive nasal reaction. This finding is in line with the study by Moscato et al⁹ in which 2 of 47 hairdressers (4.2%) with suspected OA had positive bronchial and nasal reactions to PPD in the SICs. The proportion of our patients' positive SIC reactions is low compared with the reports of OA caused by persulfate salts.^{9,10} This may be in part explained by the variation of patient material and different SIC indications in these units. In addition, in our clinic, the duration of SIC with oxidative hair dye was limited to 30 minutes. Prolonged challenges might have produced more positive reactions, and therefore some cases of OA or OR due to hair dyes might have been missed.⁵⁰ Nevertheless, we assume the low proportion of positive bronchial and nasal reactions among our patients most likely indicates that OA and OR to oxidative hair dyes are rare in hairdressers with respiratory symptoms. Of note, various airborne agents are simultaneously present in hairdressing salons. Therefore, it is difficult to distinguish respiratory diseases caused by hair dyes from other work-related respiratory diseases. Because of our selected patient material, we are not able to estimate the population prevalence of PPD-induced asthma, rhinitis, or contact urticaria based on our data.

There is a lack of internationally accepted scoring systems and criteria of positive nasal reactions. Several ratings and criteria have been previously published.^{44,51–53} Most ratings use symptom scoring as the main criteria and usually include some requirement for nasal obstruction to confirm the diagnosis of OR. The Hytola and Sala scoring system⁴⁴ we used in SIC rhinitis interpretations did not require nasal blockage for positivity, in contrast to some other international criteria.^{51,52} The sensitivity of nasal scoring in SIC is currently unknown, especially concerning chemicals. In the literature, SIC–nasal provocation test is usually used as the criterion standard test. Secretion weight measurement as the objective tool to evaluate nasal reactions has been used by Pirila et al.⁵⁴ In their comparisons of objective parameters to evaluate provocation test reactions, the secretion parameters were found to be slightly superior to the nasal blockage parameters. Secretion weight measurements have also been used for physiologic nasal measurements⁵⁵ and in medication studies.⁵⁶

Our patients were tested with work simulation SICs in which oxidative hair dyes were mixed with oxidizing agents. Nebulization of PPD as a challenge method has been previously reported.^{9,33} Using a work simulation, the exposure during SICs mimics the exposure at work, in which not only PPD is present but also other para-amino compounds, hydrogen peroxide oxidants, and other hair dye product components that may play a role in the bronchial or nasal reaction. Six of our 9 patients diagnosed as having an occupational

respiratory disease caused by oxidative hair dyes also underwent an SIC with oxidized bleaching agents that contained persulfates, all of them with negative results. Because similar oxidants are used with persulfate products, it is unlikely that the positive SIC reactions to oxidative hair dyes would have been solely caused by the oxidants. Nevertheless, the oxidation of hair dye may have some effect on the SIC result. The pattern of our patients' asthmatic SIC reaction varied, as has been reported in OA to persulfates.^{9,10}

To our knowledge, studies on the mechanisms of immediate PPD allergy are lacking. Regarding delayed allergy, PPD has been considered a prohaptan, and one or more of the oxidation products and metabolites of PPD regarded as the real allergens.⁵⁷ More recent studies suggest that both PPD and its metabolites are involved in the sensitization and elicitation of allergic contact dermatitis caused by PPD.^{58,59} In practice, the oxidative hair dyes are applied in the presence of hydrogen peroxide. In our study, patient 1 reacted positively in the open skin test, displaying urticarial wheals in reaction to hair and eyelash dyes mixed with an oxidant that contained hydrogen peroxide but not to the hair dye tested without the oxidant. Interestingly, hydrogen peroxide has been shown in vitro to inactivate arylamine *N*-acetyltransferase 1, an enzyme expressed in Ia keratinocytes and involved in the *N*-acetylation of PPD, which is considered a detoxification pathway for PPD.⁶⁰ Therefore, the presence of hydrogen peroxide might temporarily decrease PPD acetylation by keratinocytes and in this way promotes the elicitation of an allergic reaction to PPD.

SPT negativity to PPD in patients with a positive response to hair dyes in SICs and in open skin testing might imply that the actual allergen is an oxidation product of PPD or some other para-amino compound present in hair dye and not PPD itself. It remains to be clarified in further studies whether SPT with oxidized PPD and oxidized hair dye products is more sensitive in detecting immediate allergy to PPD and related para-amino compounds than SPT with unoxidized PPD and hair dye products.

In conclusion, PPD and the related para-amino compounds in oxidative hair dyes may cause occupational allergic and non-immunologic contact urticaria, asthma, and rhinitis among hairdressers. These diseases should still be considered if a hairdresser experiences symptoms associated with hair dyeing, despite a negative SPT result to PPD. Although we detected positive SPTs with HSA-conjugated PPD and TDS in one patient, SPTs with PPD or an unoxidized hair dye product seem insensitive in detecting immediate hypersensitivity. The SIC is a useful method for identifying hair dyes as the cause of OA and OR among hairdressers with work-related respiratory symptoms.

References

- [1] Brisman J, Albin M, Rylander L, et al. The incidence of respiratory symptoms in female Swedish hairdressers. *Am J Ind Med*. 2003;44:673–678.
- [2] Leino T, Tammilehto L, Luukkainen R, Nordman H. Self reported respiratory symptoms and diseases among hairdressers. *Occup Environ Med*. 1997;54:452–455.
- [3] Lind ML, Albin M, Brisman J, et al. Incidence of hand eczema in female Swedish hairdressers. *Occup Environ Med*. 2007;64:191–195.
- [4] Lysdal SH, Sosted H, Andersen KE, Johansen JD. Hand eczema in hairdressers: a Danish register-based study of the prevalence of hand eczema and its career consequences. *Contact Dermatitis*. 2011;65:151–158.
- [5] Leino T, Kahkonen E, Saarinen L, Henriks-Eckerman ML, Paakkulainen H. Working conditions and health in hairdressing salons. *Appl Occup Environ Hyg*. 1999;14:26–33.
- [6] Mounier-Geyssant E, Oury V, Mouchot L, Paris C, Zmirou-Navier D. Exposure of hairdressing apprentices to airborne hazardous substances. *Environ Health*. 2006;5:23.
- [7] Blainey AD, Ollier S, Cundell D, Smith RE, Davies RJ. Occupational asthma in a hairdressing salon. *Thorax*. 1986;41:42–50.
- [8] Pepys J, Hutchcroft BJ, Breslin AB. Asthma due to inhaled chemical agents: persulfate salts and henna in hairdressers. *Clin Allergy*. 1976;6:399–404.
- [9] Moscato G, Pignatti P, Yacoub MR, Romano C, Spezia S, Perfetti L. Occupational asthma and occupational rhinitis in hairdressers. *Chest*. 2005;128:3590–3598.
- [10] Munoz X, Cruz MJ, Orriols R, Bravo C, Espuga M, Morell F. Occupational asthma due to persulfate salts: diagnosis and follow-up. *Chest*. 2003;123:2124–2129.

- [11] Moscato G, Galdi E. Asthma and hairdressers. *Curr Opin Allergy Clin Immunol*. 2006;6:91–95.
- [12] Leino T, Tammilehto L, Hytonen M, Sala E, Paakkulainen H, Kanerva L. Occupational skin and respiratory diseases among hairdressers. *Scand J Work Environ Health*. 1998;24:398–406.
- [13] Yazar K, Boman A, Liden C. Potent skin sensitizers in oxidative hair dye products on the Swedish market. *Contact Dermatitis*. 2009;61:269–275.
- [14] Kligman AM. The identification of contact allergens by human assay, 3: the maximization test: a procedure for screening and rating contact sensitizers. *J Invest Dermatol*. 1966;47:393–409.
- [15] Thyssen JP, Carlsen BC, Sosted H, Menne T, Johansen JD. Frequency of p-phenylenediamine sensitization among Danish eczema patients tested between 1985 and 2007. *Contact Dermatitis*. 2008;59:184–185.
- [16] Thyssen JP, White JM. Epidemiological data on consumer allergy to p-phenylenediamine. *Contact Dermatitis*. 2008;59:327–343.
- [17] Krasteva M, Bons B, Ryan C, Gerberick GF. Consumer allergy to oxidative hair coloring products: epidemiologic data in the literature. *Dermatitis*. 2009;20:123–141.
- [18] Schnuch A, Lessmann H, Frosch PJ, Uter W. Para-phenylenediamine: the profile of an important allergen: results of the IVDK. *Br J Dermatol*. 2008;159:379–386.
- [19] Chan YC, Ng SK, Goh CL. Positive patch-test reactions to para-phenylenediamine, their clinical relevance and the concept of clinical tolerance. *Contact Dermatitis*. 2001;45:217–220.
- [20] Malvestio A, Bovenzi M, Hoteit M, et al. p-Phenylenediamine sensitization and occupation. *Contact Dermatitis*. 2011;64:37–42.
- [21] Guerra L, Tosti A, Bardazzi F, et al. Contact dermatitis in hairdressers: the Italian experience. *Contact Dermatitis*. 1992;26:101–107.
- [22] Valks R, Conde-Salazar L, Malfeito J, Ledo S. Contact dermatitis in hairdressers, 10 years later: patch-test results in 300 hairdressers (1994 to 2003) and comparison with previous study. *Dermatitis*. 2005;16:28–31.
- [23] Patel S, Basketter DA, Jefferies D, et al. Patch test frequency to p-phenylenediamine: follow up over the last 6 years. *Contact Dermatitis*. 2007;56:35–37.
- [24] McFadden JP, White IR, Frosch PJ, Sosted H, Johansen JD, Menne T. Allergy to hair dye. *BMJ*. 2007;334:220.
- [25] Calnan C. Hair dye reaction. *Contact Dermatitis Newsletter*. 1967;1:16.
- [26] Temesvari E. Contact urticaria from paraphenylenediamine. *Contact Dermatitis*. 1984;11:125.
- [27] Edwards EK Jr, Edwards EK. Contact urticaria and allergic contact dermatitis caused by paraphenylenediamine. *Cutis*. 1984;34:87–88.
- [28] Wong GA, King CM. Immediate-type hypersensitivity and allergic contact dermatitis due to para-phenylenediamine in hair dye. *Contact Dermatitis*. 2003;48:166.
- [29] Fukunaga T, Kawagoe R, Hozumi H, Kanzaki T. Contact anaphylaxis due to para-phenylenediamine. *Contact Dermatitis*. 1996;35:185–186.
- [30] Mavroleon G, Begishvili B, Frew AJ. Anaphylaxis to hair dye: a case report. *Clin Exp Allergy*. 1998;28:121–122.
- [31] Goldberg BJ, Herman FF, Hirata I. Systemic anaphylaxis due to an oxidation product of p-phenylenediamine in a hair dye. *Ann Allergy*. 1987;58:205–208.
- [32] Belton AL, Chira T. Fatal anaphylactic reaction to hair dye. *Am J Forensic Med Pathol*. 1997;18:290–292.
- [33] Silberman DE, Sorrell AH. Allergy in fur workers with special reference to paraphenylenediamine. *J Allergy*. 1959;30:11–18.
- [34] Birnie AJ, English JS. Immediate hypersensitivity to paraphenylenediamine. *Contact Dermatitis*. 2007;56:240.
- [35] Gelfand HH. Respiratory allergy due to chemical compounds encountered in the rubber, lacquer, shellac, and beauty culture industries. *J Allergy*. 1963;34:374–381.
- [36] Airaksinen LK, Tuomi TO, Tuppurainen MO, Lauerma AI, Toskala EM. Inhalation challenge test in the diagnosis of occupational rhinitis. *Am J Rhinol*. 2008;22:38–46.
- [37] Howe W, Venables KM, Topping MD, et al. Tetrachlorophthalic anhydride asthma: evidence for specific IgE antibody. *J Allergy Clin Immunol*. 1983;71:5–11.
- [38] American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med*. 1995;152:1107–1136.
- [39] Sovijarvi AR, Malmberg LP, Reinikainen K, Ryttilä P, Poppius H. A rapid dosimetric method with controlled tidal breathing for histamine challenge: repeatability and distribution of bronchial reactivity in a clinical material. *Chest*. 1993;104:164–170.
- [40] Burge PS. Single and serial measurements of lung function in the diagnosis of occupational asthma. *Eur J Respir Dis*. 1982;123:47–59.
- [41] ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med*. 2005;171:912–930.
- [42] Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med*. 2011;184:602–615.
- [43] Vandenplas O, Malo JL. Inhalation challenges with agents causing occupational asthma. *Eur Respir J*. 1997;10:2612–2629.
- [44] Hytonen M, Sala E. Nasal provocation test in the diagnostics of occupational allergic rhinitis. *Rhinology*. 1996;34:86–90.
- [45] Airaksinen L, Tuomi T, Vanhanen M, Voutilainen R, Toskala E. Use of nasal provocation test in the diagnostics of occupational rhinitis. *Rhinology*. 2007;45:40–46.
- [46] Sahoo B, Handa S, Penchallaiah K, Kumar B. Contact anaphylaxis due to hair dye. *Contact Dermatitis*. 2000;43:244.
- [47] Pasche-Koo F, French L, Piletta-Zanin PA, Hauser C. Contact urticaria and shock to hair dye. *Allergy*. 1998;53:904–905.
- [48] Lahti A, Vaananen A, Kokkonen EL, Hannuksela M. Acetylsalicylic acid inhibits non-immunologic contact urticaria. *Contact Dermatitis*. 1987;16:133–135.
- [49] Siracusa A, Desrosiers M, Marabini A. Epidemiology of occupational rhinitis: prevalence, aetiology and determinants. *Clin Exp Allergy*. 2000;30:1519–1534.
- [50] D'alpaos V, Vandenplas O, Ervart G, Jamart J. Inhalation challenges with occupational agents: threshold duration of exposure. *Respir Med*. 2013;107:739–744.
- [51] Dordal MT, Lluch-Bernal M, Sanchez MC, et al. Allergen-specific nasal provocation testing: review by the rhinoconjunctivitis committee of the Spanish Society of Allergy and Clinical Immunology. *J Investig Allergol Clin Immunol*. 2011;21:1–12.
- [52] Gosepath J, Amedee RG, Mann WJ. Nasal provocation testing as an international standard for evaluation of allergic and nonallergic rhinitis. *Laryngoscope*. 2005;115:512–516.
- [53] Litvyakova LI, Baraniuk JN. Nasal provocation testing: a review. *Ann Allergy Asthma Immunol*. 2001;86:355–364.
- [54] Pirilä T, Nuutinen J. Acoustic rhinometry, rhinomanometry and the amount of nasal secretion in the clinical monitoring of the nasal provocation test. *Clin Exp Allergy*. 1998;28:468–477.
- [55] Naclerio RM, Baroody FM. Response of nasal mucosa to histamine or methacholine challenge: use of a quantitative method to examine the modulatory effects of atropine and ipratropium bromide. *J Allergy Clin Immunol*. 1992;90:1051–1054.
- [56] Stuebner P, Horak F, Ziegelmayer R, et al. Effects of rupatadine vs placebo on allergen-induced symptoms in patients exposed to aeroallergens in the Vienna Challenge Chamber. *Ann Allergy Asthma Immunol*. 2006;96:37–44.
- [57] Krasteva M, Nicolas JF, Chabeau G, et al. Dissociation of allergenic and immunogenic functions in contact sensitivity to para-phenylenediamine. *Int Arch Allergy Immunol*. 1993;102:200–204.
- [58] Coulter EM, Farrell J, Mathews KL, et al. Activation of human dendritic cells by p-phenylenediamine. *J Pharmacol Exp Ther*. 2007;320:885–892.
- [59] Coulter EM, Jenkinson C, Wu Y, et al. Activation of T-cells from allergic patients and volunteers by p-phenylenediamine and Bandrowski's base. *J Invest Dermatol*. 2008;128:897–905.
- [60] Atmane N, Dairou J, Paul A, Dupret JM, Rodrigues-Lima F. Redox regulation of the human xenobiotic metabolizing enzyme arylamine N-acetyltransferase 1 (NAT1): reversible inactivation by hydrogen peroxide. *J Biol Chem*. 2003;278:35086–35092.