

Periorbital Contact Sensitization

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- **PURPOSE:** To identify frequency and pattern of contact sensitization among patients with periorbital dermatitis.
- **DESIGN:** Cross-sectional retrospective investigation of 1247 patients referred for patch testing over a 17-year period.
- **METHODS:** Data were collected for patients undergoing patch testing to the standard and customized trays between January 1990 and December 2006 at the Massachusetts General Hospital, Contact Dermatitis Clinic. Our study group consisted of 266 patients affected by periorbital dermatitis. Findings were compared to 981 referrals without periorbital dermatitis (controls). Patch test results were read after 48 and 72 hours and classified as allergic, questionable, irritant, or negative. Statistical analyses were carried out by using χ^2 test and Fisher exact test.
- **RESULTS:** General epidemiologic data among periorbital dermatitis patients showed significant predominance of female gender (87.6%) and of individuals aged 40 to 59 years (45.9%). Nickel (16.5%) and fragrance mix (13.2%) were the top-ranking sensitizers. Ingredients of topical ophthalmologic products did not result in significant sensitization. Comparison of the periorbital dermatitis group to the controls did not reveal significant differences in sensitization pattern. Patch testing confirmed the likelihood of allergic contact dermatitis in 50.8% of the periorbital dermatitis patients tested.
- **CONCLUSIONS:** Allergic contact dermatitis is a common cause of periorbital dermatitis. Patch testing should be considered in all patients with periorbital dermatitis when suspecting contact allergy in order to identify and avoid offending allergens. (Am J Ophthalmol 2010;xx:xxx. © 2010 by Elsevier Inc. All rights reserved.)

PERIORBITAL DERMATITIS IS AN INFLAMMATORY PROCESS that is pruritic, produces significant edema and scaling of the periorbital region, and can be chronic.¹ These characteristics can induce scratching and manipulation of the periorbital skin with possible sequelae including infection, disturbance in normal tearing dynamics, and possible loss of eyelashes. Etiologies include allergic or irritant contact dermatitis, atopic eczema, seborrheic dermatitis, rosacea, tinea faciei, or dermatomyositis.²⁻⁵

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Furthermore, the chronic use of topical corticosteroids to treat eczema in the periorbital skin can have serious effects such as cataract formation and glaucoma. Allergic contact dermatitis is common around the eyes.^{6,7} This may be related to the extremely thin nature of the periorbital skin, which facilitates penetration of potential allergens. Although allergic contact dermatitis of the periorbital area is not life threatening and affects only a small body area, it decreases quality of life through its often chronic, habitually relapsing course; its impact on esthetic well-being; and most importantly its effect on vision due to edema. Early detection and removal of the offending agent is paramount to prevent chronicity and this can be attained using patch testing as the diagnostic tool. We report a retrospective review of the positive patch tests and relevancies in 266 patients with periorbital dermatitis evaluated between January 1990 and December 2006 at a representative North American patch test clinic. Test results were compared to 981 referrals without involvement of the periorbital area.

MATERIALS AND METHODS

DATA WERE COLLECTED FROM CHARTS REVIEWED FOR 1247 patients referred for patch testing. This group consisted of 266 patients with a primary complaint of periorbital dermatitis (including 166 patients with isolated periorbital dermatitis) and 981 individuals without periorbital dermatitis (controls). All individuals underwent patch testing to the standard (29 allergens) and in special cases to selected customized trays at the Massachusetts General Hospital, Contact Dermatitis Clinic between January 1990 and December 2006. Patch testing and reading was conducted by standardized technique in accordance with international recommendations, applying Finn chambers (Epitest Ltd Oy, Tuusula, Finland) affixed with Scanpor tape (Norgesplaster A/S, Vennesla, Norway) to the upper back.⁸ Allergens were purchased from Hermal (Reinbek, Germany). Tests remained in place for 48 hours and test sites were initially evaluated after 48 and 72 hours and in a few cases again at 96 hours and/or 7 days following placement. In this analysis only 48- and 72-hour readings were included. In selected cases adjusted patch test methods were applied on stripped skin to increase the test sensitivity. Those results were not included in this analysis. All interviews and interpretations of patch test reactions over the whole study period were performed by a single observer (E.G.). Positive patch tests reactions were graded

TABLE 1. General Information of Patch-Tested Population Referred With and Without Periorbital Dermatitis With Regard to Gender, Age, and Atopic Disposition

	Periorbital Dermatitis	95% Confidence Interval	Controls	95% Confidence Interval	P Value Periorbital Dermatitis vs Controls
N	266		981		
Females, n	233 (87.6%)	(83.4, 91.3)	641 (65.3%)	(62.3, 68.2)	<.005
Average age in years	44.0	(38.3, 50.2)	46.8	(43.7, 50)	.01
Atopic disposition, n	40 (15.0%)	(11.0, 19.5)	132 (13.5%)	(11.5, 15.8)	.507

TABLE 2. Most Frequent Allergens in Patients With Periorbital Dermatitis With Details on Clinical Relevance and Comparison to the Control Group

Allergen	Main Sources	Periorbital Dermatitis Sensitized, n (%)	95% Confidence Interval	Periorbital Dermatitis Relevant Test Results in %	Controls Sensitized, n (%)	95% Confidence Interval	P Value Periorbital Dermatitis vs Controls
Nickel sulfate	Metals, cosmetics (mascara)	44 (16.5%)	(12.3, 21.2)	86.4	138 (14.1%)	(12.2, 16.6)	.352
Fragrance mix	Fragrance in cosmetics	35 (13.2%)	(9.7, 17.8)	54.3	160 (16.3%)	(14.2, 18.9)	.184
Cobalt chloride, 6H ₂ O	Metals	23 (8.6%)	(5.6, 12.3)	69.6	70 (7.2%)	(5.7, 8.9)	.431
Balsam of Peru	Fragrance in cosmetics, creams	19 (7.1%)	(4.3, 10.5)	57.9	125 (12.7%)	(10.9, 15.1)	.01
Quaternium 15	Preservative in cosmetics	19 (7.1%)	(4.3, 10.5)	84.2	62 (6.3%)	(5.0, 8.0)	.667
4-phenylenediamine base	Hair dyes, henna paintings	13 (4.9%)	(2.9, 8.2)	53.8	34 (3.5%)	(2.5, 4.8)	.306
Thiuram mix	Accelerator in rubber products	12 (4.5%)	(2.3, 7.3)	75.0	50 (5.1%)	(4.0, 6.8)	.668
Colophony	Cosmetics, mascara	12 (4.5%)	(2.3, 7.3)	58.3	39 (4.0%)	(2.9, 5.4)	.724
Formaldehyde	Preservative, disinfectant, antiseptic	10 (3.8%)	(2.1, 6.8)	80.0	64 (6.5%)	(5.1, 8.3)	.083
Thimerosal	Preservative in vaccines, eye drops	10 (3.8%)	(1.6, 5.9)	90.0	27 (2.8%)	(1.3, 4.8)	.089
Potassium dichromate	Leather, cement	9 (3.4%)	(1.8, 6.3)	66.7	36 (3.7%)	(2.7, 5.1)	.803
Neomycin sulfate	Topical antibiotics	9 (3.4%)	(1.8, 6.3)	22.2	50 (5.1%)	(4.0, 6.8)	.228
N-isopropyl-N-phenyl-4-phenylenediamine	Rubber products	8 (3.0%)	(1.3, 5.4)	62.5	38 (3.9%)	(2.8, 5.3)	.506
Wool alcohols	Vehicle in creams, cosmetics	8 (3.0%)	(1.3, 5.4)	87.5	50 (5.1%)	(4.0, 6.8)	.142
Paraben mix	Preservative in creams, cosmetics	8 (3.0%)	(1.3, 5.4)	62.5	31 (3.2%)	(2.2, 4.5)	.874
Epoxy resin	Adhesives, dental material	7 (2.6%)	(1.1, 4.9)	85.7	27 (2.8%)	(1.9, 4.0)	.891
Carba mix	Rubber products	5 (1.9%)	(0.8, 4.3)	60.0	29 (3.0%)	(2.2, 4.3)	.344
Phenylmercuric acetate	Preservative in meds and cosmetics	5 (1.9%)	(0.8, 4.3)	80.0	25 (2.5%)	(1.7, 3.6)	.528
Balsam of Tolu	Fragrance in cosmetics	4 (1.5%)	(0.4, 3.3)	25.0	25 (2.5%)	(1.7, 3.6)	.316
Methylchloroisothiazolinone/methylisothiazolinone (3:1 in water)	Preservative in cosmetics, meds	4 (1.5%)	(0.4, 3.3)	75.0	17 (1.7%)	(1.0, 2.6)	1

according to international guidelines⁸ as + (infiltrated erythema, nonvesicular), ++ (edematous or vesicular), or +++ (bullous and/or erosion). Ambiguous or irritant reactions were considered negative. Relevance of positive results was determined by assessment of past history of contact with the allergen and whether expressed symptoms

were consistent with the clinical picture and history. Probable, possible, and certain relevance were pooled under “relevant” while past, unknown, and not applicable were considered as “nonrelevant.” Patients were instructed about possible allergen sources and how to avoid them. A follow-up visit was used to evaluate outcomes. The absence

of further skin complaints and a partial or complete recovery when strictly avoiding the positive-tested allergens was confirmatory for the diagnosis of allergic contact dermatitis. A re-challenge to the contact allergens was not performed. Further common diagnoses of periorbital skin changes in case of negative or nonrelevant patch test results included atopic dermatitis (personal or family history of flexural eczema), irritant contact dermatitis (dermatitis at the site of contact with presence of a substance known to be an irritant), seborrheic dermatitis (papulopustular disorder on sebum-rich hair-bearing areas), rosacea (papulopustular erythematous, acne-like rash, associated with telangiectasia), and urticaria (transient pruritic erythematous and edematous plaques). For age-related data analysis, individuals were categorized into age groups of ≤ 19 , 20–39, 40–59, and ≥ 60 years.

Data were recorded, retrieved, and evaluated using a computer database (Microsoft Access 2000, Seattle, Washington, USA). Statistical analysis was performed with SPSS 15.0 (SPSS Inc, Chicago, Illinois, USA). Frequencies were compared using the χ^2 test and Fisher exact test where appropriate. Statistical analysis was done on the 20 most frequent allergens that were found for 266 patients with periorbital dermatitis. The multiple level of significance was 0.05. To adapt for multiple testing, the level of significance for allergens tested was adjusted to $\alpha \leq 0.003$ (Bonferroni correction of factor 20).

RESULTS

PATIENTS PATCH TESTED FOR PERIORBITAL DERMATITIS made up 21.3% (266/1247) of investigated individuals in this 17-year period of observation. Two hundred thirty-three female patients, aged 8–78 years, and 33 men, between 17 and 79 years, were evaluated. As shown in Table 1, predominance of female gender in the periorbital dermatitis group (87.6%) was statistically significant ($P < .005$) compared to those patients tested for reasons other than periorbital dermatitis (65.3%). Also, patients referred for evaluation of periorbital dermatitis were on average statistically significantly younger than the controls. Most individuals belonged to the age group 40–59 years (45.9%), followed by 20–39 years (38.3%). Children/adolescents and older patients were infrequently seen; only 1.9% of referrals were ≤ 19 and 13.9% were ≥ 60 years respectively. At the initial visit, 15% of patients reported an atopic history, being defined as the presence of at least 1 of the following conditions: atopic dermatitis, allergic rhinoconjunctivitis, or allergic asthma. Sensitized individuals showed on average 2.0 positive reactions. Leading sensitizers were nickel sulfate, fragrance mix, cobalt chloride, balsam of Peru, and quaternium 15 (Table 2). Among 20 most frequent allergens in patients with periorbital dermatitis, no statistically significant gender-related predominance was observed (data not shown). Highest rele-

vance was evaluated for thimerosal, wool alcohols, nickel sulfate, and epoxy resin. Comparison of sensitization to common allergens among patients with periorbital dermatitis and those without did not show statistically significant differences. For the various age groups, leading allergens were the following: ≤ 19 years, thimerosal and fragrance mix; 20–39 years, nickel sulfate and fragrance mix; 40–59 years, nickel sulfate and fragrance mix. Individuals ≥ 60 showed highest sensitization rates for fragrance mix and balsam of Peru. Further details of sensitization rates are listed in Table 2. Most common final diagnoses in patients with periorbital dermatitis and those without were allergic contact dermatitis (50.8% vs 43.4%), followed by atopic dermatitis (26.3% vs 20.0%) and atopic dermatitis with relevant allergic contact dermatitis (4.2% vs 3.2%). The concomitant diagnoses of allergic contact dermatitis and atopic dermatitis were significantly more common in the periorbital dermatitis group ($P < .05$), while irritant contact dermatitis dominated in the control group (4.4% vs 0.8%; $P < .005$). Further common etiologies included psoriasis (periorbital group 2.3%, controls 3.2%), seborrheic dermatitis (1.4% vs 1.0%), rosacea (0.8% vs 0.7%), and urticaria (0.4% vs 1.2%). The remaining 13% of individuals evaluated for periorbital dermatitis were merged under “other diagnoses” and included less common diseases such as protein contact dermatitis, dermatomyositis and angioedema.

DISCUSSION

THE NUMBER OF PATIENTS REFERRED TO OUR CLINIC WITH periorbital dermatitis (21.3%), suspicious for allergic contact diagnosis, was higher than previously reported in the literature describing rates between 3% and 13% for periorbital and eyelid dermatitis, respectively.^{1,3,4,9} Variations in these numbers can be attributed to different levels of sensitization in the countries and also to the specialization of certain centers seeing a more or less select group of patients at the end of a referral process. The majority of referrals were found in the 20–59 age group, while fewer patients were seen in groups of younger or older patients. Small numbers of young patients < 20 years were also observed in a study conducted by Amin and Belsito.⁴ In contrast to our results, their proportion of individuals > 60 years was higher (33.4%) compared to ours (13.9%). It remains unclear why this difference is occurring in the older age group.

Predominance of female gender among individuals suffering from periorbital dermatitis is well known from the literature.^{3,6} Our ratio of 87.6% is consistent with observations by Guin (90%),⁷ Amin and Belsito (88.6%),⁴ and Valsecchi and associates (90%).¹ These findings were attributed to a higher application of cosmetics and topical products to the face, and especially to the periorbital area.^{1,4} In accordance with this assumption, leading sensi-

tizers we found included fragrances, metals, and preservatives. Surprisingly, no significant difference was observed when looking at gender-related sensitization pattern or when comparing important sensitizers from our controls. Stable prevalence of commonly seen allergens likely reflects their extensive distribution in industry and everyday life. Contrary to our finding, Amin and Belsito⁴ observed a significant increase in contact allergy to fragrances, oleamidopropyl dimethylamine, benzalkonium chloride, and tosylamide formaldehyde resin in patients with eyelid dermatitis compared to those without. A comparison to their study may be limited by differences in the definition of levels of significance, which they defined as $P \leq .05$, in contrast to our results using a significance level of $P \leq .003$.

Within leading allergens, nickel sulfate showed the highest numbers of sensitized and relevant reactions. Sensitization to nickel can be caused by direct application of nickel-containing eye cosmetics such as eye shadows,¹⁰ mascara,¹¹ or eye pencils,¹² or by contact to metal-containing eyeglass frames or eyelash curlers. Because most cosmetic products do not list nickel as an ingredient, exposure to nickel via cosmetics has been thought to result from contamination during manufacture, or from the metal casing, where it is kept in, respectively.^{1,4} In addition, one must always consider the possibility of an accidental transfer, mostly by the hands^{2,7} (ectopic dermatitis). It can be assumed that the accidental transfer by the hands does elicit the majority of cases of nickel-induced periorbital dermatitis. Because of the thin nature of periorbital skin, sensitization might manifest clinically in this area. Wide distribution of nickel-containing metal products in the environment explains the high sensitization rate among our test population and the controls. Similar findings in patients with periorbital/eyelid eczema have been presented earlier.^{1-3,9} In contrast to our results showing a high relevance for nickel in the periorbital area, other authors described antithetical results. Valsecchi and associates¹ could not establish relevance in any of 63 positive reactions to nickel in patients with eyelid dermatitis. Shah and associates⁹ described only 1 out of 4 sensitizations as a relevant reaction to this metal.

Similar to nickel, thimerosal yielded highly relevant results. The majority of patients tested for thimerosal belonged to the age group ≤ 19 years, where it was found to be the leading allergen. Thus, it can be hypothesized that sensitizations were more likely to be related to vaccination in childhood and not to the use of ophthalmic products. This hypothesis would be supported by our data, which did not show significant differences in sensitization when comparing to the controls. Formerly used as a preservative in multidose-unit vaccines,¹³ thimerosal yielded highest contact sensitization rates in children/adolescents, but clinical relevance was stated to be low.¹⁴ Furthermore, it was found as an additive in eye drops or ear drops, contact lens solutions, mascara, and make-up. Because of possible side effects caused by ethyl mercury as a metabolizing

product of thimerosal,^{13,15} the Centers for Disease Control and Prevention (CDC) issued a precautionary recommendation and manufacturers were asked to reduce or eliminate thimerosal from vaccines in 1999.¹⁵ Therefore thimerosal is likely of historic relevance, although retaining the knowledge of its significant potential for allergenicity is important. Since our study reflects results of patients tested between 1990 and 2006, our cases occurred during a time before precautionary recommendations were given and sensitization rates displayed in this study presumably show higher sensitization rates than would be expected today. The approach among ophthalmologists to use preservative-free eye drops (eg, single-dose) will probably reduce the sensitization to this allergen, as well. Recently, the North American Contact Dermatitis Group removed thimerosal from the standard tray because of false-positive reactions, its low relevance in the general patch test data, and the reduced utilization attributable to the CDC recommendation. At present, most prescription ophthalmic preparations use the quaternary ammonium compounds, primarily benzalkonium chloride, as a preservative since it has been shown to have a very low allergenicity. One study demonstrated a rate of sensitivity of 0.7% for benzalkonium chloride compared to 11.3% for thimerosal.¹⁶ A review of the literature to identify prevalence of allergy to ophthalmic preservatives stated that most of the reactions to benzalkonium chloride were irritant in nature while reactions to thimerosal were allergic.¹⁷ In our study, only 2 of 266 patients were identified with type IV sensitization against benzalkonium chloride, resulting in a total rate of sensitization of 0.8% (data not shown). Thus, even among the preselected group investigated in this study for periorbital dermatitis, benzalkonium chloride cannot be regarded as a common sensitizer.

Other high-ranking allergens from our investigation included fragrance mix and the cross-reacting balsam of Peru.¹⁸ Sensitization rates of 13.2% (35/266 patients) for fragrance mix and 7.1% (19/266 patients) for balsam of Peru are similar to other studies describing rates of positive reactions of 8% to 20% for fragrance mix^{1,3,9} and 3.3% to 8% for balsam of Peru.^{1,3,9} As the face and the hands are the most-affected body sites for fragrance allergy,^{19,20} a transfer of the agent from the hand to the face might also be a relevant source of sensitization.²

In our study 50.8% (135/266) of tested individuals with periorbital dermatitis were diagnosed with allergic contact dermatitis after patch testing, followed by atopic dermatitis and others. Similar to sensitization rates of previous studies showing allergic contact dermatitis in rates of 43.8% to 72%,^{1,4,9,21} it was the most frequent final diagnosis among individuals tested for periorbital dermatitis. Despite the fact that allergic contact dermatitis and atopic dermatitis are the 2 most common diagnoses in patients with periorbital dermatitis, other diagnoses such as rosacea, seborrheic dermatitis, tinea faciale, dermatomyositis, lupus erythematosus, erysipelas, and zoster ophthalmicus should be considered.

The following limitations to this study need to be recognized. Our study sample was drawn from patients who were referred to a dermatologist for patch testing; as such, they may not be representative of the general population.

Secondly, patch testing is conventionally conducted on the upper back and it is possible that penetration of allergens and susceptibility of truncal skin differs from periorbital skin such that some of the weaker allergens inducing reactions in the periorbital area might not show up in the upper back. Thirdly, in this analysis only 72-hour readings were incorporated. Thus we might have overlooked some late-reacting allergens.

In summary, allergic contact dermatitis represents a leading etiologic cause of dermatitis of the periorbital area, particularly in females. Therefore, patch testing should be considered a standard diagnostic tool. Most common allergens were similar to those that are seen in general patch test populations, such as metals, fragrances and preservatives. The prevalence of sensitization to ophthal-

mic allergens is less than those to environmental allergens, most likely a result of the increased use of preservative-free (eg, single-dose vials) ophthalmics. Whenever contact sensitization against ophthalmic drops or ointments is suspected, the repeated open application test may be used as a preliminary, simple test. In this test, the incriminated ophthalmic product(s) have to be applied to the forearm twice a day, repeatedly over a period of 5 to 7 days. Redness, infiltration, and swelling may suggest a contact allergy that can be confirmed by standard patch testing. For determination of possible contact sensitization referral to a specialist is appropriate.

If conventional patch testing at the upper back does not confirm allergic contact sensitization to suspicious allergens, in certain cases adjustment of patch test methodology might be necessary. Sensitivity, but also the possibility of false-positive results because of a heightened irritancy, may be increased by tape stripping, enlarged test areas, or higher patch test concentrations.

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Biosketch

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Biosketch

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