

Recommendations for a Screening Series for Allergic Contact Eyelid Dermatitis

Elise M. Herro, MD,* Mohammed L. Elsaie, MD,† Rajiv I. Nijhawan, MD,‡ and Sharon E. Jacob, MD*

Background: Although allergic contact dermatitis of the eyelids is a common condition, limited information is available regarding the selection of patch-testing chemicals for proper evaluation.

Objective: The purpose of this analysis was to evaluate the relevance of allergens responsible for allergic eyelid dermatitis among a series of patch-tested patients attending our clinic at the University of Miami and compare these results to published studies in the literature.

Methods: Data were retrospectively reviewed for eyelid-only dermatitis from clinically relevant patch-test evaluations performed between December 2004 and January 2007.

Results: Formaldehyde was the most frequently encountered antigen, accounting for 45.83% (11/24) of the cases, followed by nickel 33.33% (8/24) and balsam of Peru (*Myroxylon pereirae*) 29.17% (7/24). In addition, not only did we find a higher prevalence of certain allergens when compared with other studies, but we identified several relevant allergens not previously reported at other referral centers.

Conclusions: The allergens found to be relevant in eyelid dermatitis vary among different regions. These data may help contribute to generating a standard screening tool to improve the detection and management of these cases.

THE SKIN of the eyelid is very delicate and thin, measuring less than 1 mm in thickness.¹ It has a very loosely bound subcutis, and on contact with irritating and allergenic chemicals, marked edema often develops, which is a characteristic feature in eyelid contact dermatitis. Quite literally, the eyelids are subjected to potentially harmful elements (UV radiation, airborne environmental allergens, and chemicals placed inadvertently from the hands or advertently through cosmeceuticals) on a daily basis. Women in our society habitually coat their eyelids with cosmetics, some of which may include mild irritants, which may be added to induce mild edema to reduce the appearance of fine wrinkles. Lastly, the eyelids are commonly challenged by systemic contact dermatitis as well.²⁻⁴

Eyelid dermatitis involves a lengthy differential diagnosis, which includes irritant contact dermatitis, atopic dermatitis (AD), psoriasis, dermatomyositis, contact urticaria, infections, cutaneous

T-cell lymphoma, and seborrheic dermatitis; allergic contact dermatitis (ACD), however, proves to be one of the most common causes.^{5,6} Moreover, it may be (and often is) superimposed on a primary nonallergic dermatitis, such as AD or seborrheic dermatitis.⁷ To date, there have been several reviews,⁸ a case series,⁹ and numerous individual case reports published on diagnostic strategies and the relevancy of allergen panels used in eyelid-only dermatitis.¹⁰⁻¹³

We retrospectively reviewed our group of patients to compare their frequencies of reaction to specific allergens to those previously documented and also to highlight allergens that may not have been previously recognized as common causes of allergic eyelid dermatitis.

PATIENTS AND METHODS

We performed a retrospective analysis of 204 adult patients who had undergone consecutive, extended series patch testing at the University of Miami between December 2004 and January 2007, searching for a subgroup of patients who met the criteria of (1) eyelid site only dermatitis, (2) a final diagnosis of ACD, and (3) a positive patch-test reaction of current clinical relevance.

Patch-testing methodology included application, followed by removal and initial evaluation at 48 hours, along with a final evaluation at 96 hours. Current relevance signified that the allergen was present in the patient's environment, the dermatitis corresponded to point(s) of contact with allergen, and the dermatitis significantly improved upon isolation/avoidance of allergen and/or recurred with rechallenge (positive use test). Patients with eyelid dermatitis

From the *Division of Dermatology, University of California, San Diego, and Rady Children's Hospital, San Diego, CA; †National Research Centre, Egypt and Department of Dermatology and Cutaneous Surgery, University of Miami, Miami, FL; and ‡Department of Dermatology, Roosevelt University, New York, NY.

Address reprint requests to Sharon E. Jacob, MD, Rady Children's Hospital, 8010 Frost St, Suite 602, San Diego, CA 92123. E-mail: SJacob@contactderm.net.

The authors have no funding or conflicts of interest to declare.

DOI: 10.1097/DER.0b013e31823d191f

© 2012 American Contact Dermatitis Society. All Rights Reserved.

TABLE 1. Relevant Contact Allergens for Patients With Eyelid Dermatitis

	Allergen	No. Relevant PPTs	% Relevant PPTs	% of Positive Reactions Cited by NACDG ⁵	% of Positive Reactions Cited by Amin and Belsito ¹⁵
1	Formaldehyde	11	35.48	1.56	6.50
2	Nickel sulfate	8	25.80	8.3	13.00
3	<i>M. pereirae</i> , (BOP)	7	22.58	8.81	—
4	Fragrance mix I	6	19.35	9.84	28.3
4	Bronopol	6	19.35	—	6.50
4	Bacitracin	6	19.35	2.07	—
7	Neomycin	5	16.13	4.67	10.90
7	Cinnamic alcohol	5	16.13	—	—
9	Benzyl alcohol	4	12.90	—	—
9	Sodium benzoate	4	12.90	—	2.20
9	Paraphenylenediamine	4	12.90	—	2.20
9	CAPB	4	12.90	2.60	2.20
13	Tosylamide formaldehyde resin	3	9.68	2.07	6.50
13	Imidazolidinyl urea	3	9.68	—	4.30
13	MMA	3	9.68	1.56	—
13	Hydroxycitronellal	3	9.68	—	—
13	Methylchloroisothiazolinone/ methylisothiazolinone	3	9.68	3.11	4.30
13	Cocamide DEA	3	9.68	—	—
20	Thimerosal	2*	6.45	—	—
20	Gold sodium thiosulfate	2*	6.45	11.40	6.50
22	Dodecyl gallate	1*	3.23	—	—

*Thimerosal, gold, and dodecyl gallate were the only 3 allergens in which all PPTs were not relevant. A total of 5 PPTs were found to thimerosal, 4 to gold, and 3 to dodecyl gallate.

PPTs, positive patch tests.

and an irrelevant, positive patch-test reaction were excluded, as were patients whose final diagnosis was determined to be an etiology other than ACD, such as AD, hay fever, and so on. These allergens were compared with previously published studies to identify top allergens and a potential screening series.

STATISTICAL ANALYSIS

All patient data were recorded, retrieved, and evaluated using a computer database. Queries and calculations were made using Microsoft software 2000 (Seattle, Wash). Statistical analysis was performed using the statistical analysis system software package (SAS Institute, Inc, Cary, NC). Positive reaction rates to our series were compared with other studies using a 2-tailed *t* test of proportion and the *Z* test of proportion. $P \leq 0.05$ was considered to be statistically significant.

RESULTS

Of 204 patch-tested patients, 32 (15.69%) met the study criteria of having eyelid-only dermatitis. Both the first and second criteria, those of a final diagnosis of ACD, were met by 31 patients (23 women and 8 men, aged 19–65 years, who self-designated themselves as racially black, 5 [16%]; white, 16 [51%]; Asian, 1 [3%], and Hispanic, 9 [29%]). Twenty-four patients (20 female and 4 male patients) then met the third criteria of a positive reac-

tion with current clinical relevance. The observed clinical relevance rate in our study was 77.4% (24/31). Table 1 lists the clinically relevant allergens.

In our group, patients were most likely to be allergic to formaldehyde (45.83%), nickel (33.33%), balsam of Peru (BOP; *Myroxylon pereirae*) (29.17%), fragrance mix (25.00%), bronopol (25.00%), and bacitracin (25.00%). The following allergens were found to be prevalent at a frequency of 3 or more in our patients and not previously documented as significant allergens for the evaluation of allergic eyelid dermatitis: cinnamic alcohol, benzyl alcohol, hydroxyl citronella, and dodecyl gallate. Allergens that identified 2 or fewer cases include cobalt, potassium dichromate, black rubber mix, diazolidinyl urea, Compositae mix, and paraben mix. Finally, the vast majority of cases occurred in women (74.2% vs 25.8%, $P < 0.001$).

DISCUSSION

Eyelid dermatitis affects a significant portion of the population, reflecting 8.6% to 18% of contact dermatitis referrals, and thus it is important to recognize potential clinically relevant allergens.¹⁵ Our results demonstrated that the vast majority of cases occur in females, which is a similar finding to the study by Amin and Belsito,¹⁵ which reported 79% to 90%. This observation may reflect the widespread use of potentially allergenic cosmetic products among women.

In our study, 31 (15%) of 204 patients had eyelid-only dermatitis and a final diagnosis of ACD, representing a higher frequency of referral for this than seen in the studies of either the North American Contact Dermatitis Group (NACDG)⁵ or Amin and Belsito¹⁵ (5.2% and 3.8%) (268/5145 and 46/1215, respectively).

The 21 relevant allergens identified by our single-center data corresponded to 15 of the allergens identified by the NACDG⁵ and Amin and Belsito¹⁵ (Table 1). Discrepancies in allergens and their prevalence may be linked to regional variations and low power from our smaller population size. In our patient subset, we found formaldehyde to be the most prevalent allergen, whereas gold and fragrance mix were the most common in the studies by the NACDG⁵ and Amin and Belsito,¹⁵ respectively.

Between 2003 and 2004, the NACDG, consisting of 13 centers, identified 268 patients with eyelid-only dermatitis in whom a final diagnosis of ACD was made. The investigators concluded that the top 26 allergens identified in this study represent a potential eyelid dermatitis screening series, as they represented 65% (175) of the cases.⁵ Furthermore, their observed clinical relevance rate of 84.3% (226/268) was slightly higher than our value of 77.4% (24/31). In 2006, Amin and Belsito¹⁵ published their 10-year retrospective analysis, showing that of 1215 patients, 105 had eyelid dermatitis, 43.8% of those having ACD.

Eleven (45.83%) of our patients demonstrated current clinically relevant positive reactions ranging from 1+ to 3+ intensity to formaldehyde, 6 to bronopol, and 3 to imidazolidinyl urea. Only 2 of the patients with contact allergy to formaldehyde underwent repeated patch testing, as the remaining patients declined after improvement. Sensitization to formaldehyde may occur through skin contact with formaldehyde, formaldehyde-releasing products (FRPs), or with clothing made from fabrics containing formaldehyde, such as permanent press or wrinkle-resistant clothing. With respect to eyelid dermatitis, many eye cosmetic or topical products contain formaldehyde or FRPs; these products are either directly applied to the eye region or transferred by contact with one's hands. For example, 2 of our patients had makeup removal lotions that contained formaldehyde, and additional products that contained FRPs included mascara (imidazolidinyl urea and diazolidinyl urea), eye shadow (imidazolidinyl urea), and shampoo (quaternium-15). Of interest, the majority of our patients were women who regularly consumed diet soda, containing aspartame, which is metabolized to formaldehyde.^{4,14} All of our patients with clinically relevant positive reactions to formaldehyde were therefore encouraged to cease consumption of diet soda as part of their avoidance regimen. Upon formaldehyde avoidance, 10 (90%) of 11 patients experienced full remission. Some of these patients refused to reintroduce the products or diet soda (provocation testing) after clearance of their dermatitis; however, when 3 patients did reintroduce diet soda, their dermatitis flared.

Nickel sensitivity, one of the most predominant sensitivities recorded in literature,¹⁶ ranked as the second most prevalent allergen in our study, which is similar to other major studies.¹⁷ Sensitivity to nickel is more often recognized in the female population

and is thought to occur from direct contact with metallic objects such as spectacle frames, eyelash curlers, or products that contain nickel as a contaminant, such as eye shadows.^{18–20} We also recognized the role of transfer of nickel particles from the hands to the eyelids (through rubbing) in several of our patients, who were frequently handling nickel-based objects (eg, identification tag chain, crochet needle, and quilting needles).

The fragrance group (*M. pereirae*, fragrance mix 1, cinnamic alcohol, hydroxycitronellal, sodium benzoate, and benzyl alcohol), which notably cross-react or coreact with each other,²¹ was found to be highly prevalent in our patients. Reactions to *M. pereirae*, or BOP, were considered relevant if products contained components of BOP or "fragrance." Whereas Cooper and Shaw²² described fewer contact allergies to fragrances mix among their eyelid dermatitis patients, other studies have found a substantially high number of patients who test positively to fragrances and fragrance mixes.^{5,15,22} These results may be explained by the predominance of females in our study population, who more often use scented/perfumed toiletries and cosmetics.

Paraphenylenediamine, used in many hair dye products,²³ caused significantly fewer positive patch tests in our series when compared with the other series. This is remarkable, given the observed prevalence of darker-colored hair dyeing and eyelid dermatitis in the patient population in the Miami area. Personal communication with our referring dermatologists suggested that patients and general dermatologists were often able to discern the link between the patient's eyelid dermatitis and hair-dyeing practices, and thus these patients would not have been evaluated at our referral center (and potentially reflects a referral bias). Cocamidopropyl betaine (CAPB), commonly found in hair products and contact lens solutions, also has been reported to cause eyelid dermatitis,^{24,25} and it ranked ninth among our most common allergens. Another allergen also found in shampoos, hair products, and lotions is methylchloroisothiazolinone, which ranked 13th in our series.

Toluene sulfonamide formaldehyde resin, found in nail varnish, is well known for its tendency to provoke an ectopic eyelid contact dermatitis.^{26–28} Among our adult patients tested, it caused a positive reaction in a total of 3 patients. Despite its relatively minor role in our series and several other major studies, it remains a commonly considered allergen in eyelid dermatitis. Methyl methacrylate (MMA), previously one of the most sensitizing acrylates, which has been banned in the United States since July 2004 for use in nail products, has been reported to be an important contributor in about 10% of cases.^{12,29} In accordance with most studies, we identified 3 cases (12.5%), 2 of which reported current use of artificial nails, whereas the third reported past use, but current use of an acrylic antichip nail polish. This led us to be concerned that MMA was being used illegally in some Miami nail salons as all 3 patients cleared with avoidance. We also considered the role of aerosolization during application of the product as a factor in these 3 patients.

In our analysis, we found 2 clinically relevant cases of eyelid dermatitis with ACD to sodium gold thiosulfate, ranking gold as

TABLE 2. Recommended Patch-Test Concentrations for Eyelid-Only Dermatitis

Compound	Concentration, %/Vehicle
Amidoamine	0.1 aq
Bacitracin	20.0 pet
BOP	25.0 pet
Benzalkonium chloride	0.1 aq
Black rubber mix	0.6 pet
Bronopol	0.5 pet
Budesonide	0.1 pet
Cinnamic aldehyde	1.0 pet
Cobalt chloride	1.0 pet
CAPB	1.0 aq
Colophony	20.0 pet
Dimethylol dimethyl hydantoin	1.0 aq/pet
Dodecyl gallate	0.25/pet
Ethyl acrylate	0.1 pet
Formaldehyde	1.0 aq
Fragrance mix I	14.0% pet
Sodium gold thiosulfate	0.5 pet
Imidazolidinyl urea	2.0 aq/pet
Lanolin alcohol	30 pet
MMA	2.0 pet
Methylchloroisothiazolinone/ methylisothiazolinone	0.01 aq
Methyldibromoglutaronitrile/ phenoxyethanol	2.0 pet
Neomycin	20.0 pet
Nickel sulfate	2.5 pet
Paraphenylenediamine	1.0 pet
Propylene glycol	30.0 aq
Quaternium-15	2.0 pet
Thimerosal	0.1 pet
Thiuram	1.0 pet
Tosylamide formaldehyde resin	10.0 pet

Aq indicates aqueous; pet, petrolatum.

20th. There was no difference in clinical significance between our series, 2 (6.5%) of 31, and the NACDG report 22 (8.2%) of 268 ($P > 0.05$).³ In addition, consistent with previously reported findings,³⁰ our patients were found to wear cosmetics containing titanium dioxide, which can absorb gold particles from jewelry and therefore cleared with cessation of use of their gold jewelry.³¹ These data support the recommendation of gold avoidance in the setting of positive patch testing to its thiosulfate allergen.

We recognize that thimerosal contact allergy has low relevancy in the general population despite high sensitization rates³²; however, we chose to include this allergen when screening for eyelid dermatitis because of its use in ophthalmologic solutions and some cosmetics and found 2 patients with currently relevant positive reactions. Of note, this ophthalmic product-associated allergen was found to be highly prevalent in patients with eyelid dermatitis in 2 large-scale European studies conducted by the information network of the departments of dermatology¹⁰ that analyzed 762

and 1053 patients, respectively, with eyelid dermatitis in Austria and Germany and by Valsecchi et al³³ in Italy.

Dodecyl gallate and cocamide diethanolamide (DEA) are considered rare allergens; however, each caused relevant positive patch tests in our study population; dodecyl gallate was found in a cream eye shadow, and cocamide DEA in an eyelid cleanser. Herbst et al⁹ reported that dodecyl gallate was an important allergen in their study of 1053 patch-tested patients with eyelid ACD and related the prevalence to exposure to cosmetics. Gallates are often used in the cosmetic industry as antioxidants to prevent the oxidation of unsaturated fatty acids in their products.³⁴ Cocamide DEA, manufactured from coconut oil, is widely used as a surface-active agent in hand gels, hand-washing liquids, shampoos, and dishwashing liquids.³⁵ Because of the extensive use of cocamide DEA and the lack of proper declaration in products, it is difficult to avoid cocamide DEA exposure.³⁶

The allergens found to be relevant in eyelid dermatitis vary among different regions, which may relate to exposure patterns. This being said, we question the role of climatic impact (eg, high humidity in Miami, Fla) on percutaneous absorption and believe further studies are warranted in this area. Furthermore, although we did find that our results were in accordance with many of the major studies in regard to the prevalence of top identified antigens, we also identified several allergens that may need to be considered in the evaluation of allergic eyelid dermatitis (specifically, cinnamic alcohol, benzyl alcohol, hydroxyl citronella, and cocamide DEA). We compared our single-center data to the reported data on eyelid allergens in an effort to generate a basic standard screening tool to improve the detection and management of these cases (Table 2), which would need to be continually updated to reflect changing exposure trends.

REFERENCES

- Skuta G, Cantor L. *Basic and Clinical Science Course: Orbit, Eyelids, and Lacrimal System*. San Francisco, CA: American Academy of Ophthalmology; 2010.
- Veien NK. General aspects of contact dermatitis. In: Froesch PJ, Mennet T, Lepoittevin JP, eds. *Contact Dermatitis*. New York, NY: Springer; 2006:201–247.
- Wolf R, Perluk H. Failure of routine patch tests results to detect eyelid dermatitis. *Cutis* 1992;49(2):133–134.
- Hill AM, Belsito DV. Systemic contact dermatitis of the eyelids caused by formaldehyde derived from aspartame? *Contact Dermatitis* 2003;49(5):258–259.
- Rietschel RL, Warshaw EM, Sasseville D, et al. North American Contact Dermatitis Group. Common contact allergens associated with eyelid dermatitis: data from the North American Contact Dermatitis Group 2003–2004 study period. *Dermatitis* 2007;18(2):78–81.
- Shah M, Lewis FM, Gawkrödger DJ. Facial dermatitis and eyelid dermatitis: a comparison of patch test and final diagnoses. *Contact Dermatitis* 1996;34(2):140–141.
- Beltrani VS, Bernstein L, Cohen DE, et al. Contact dermatitis: a practice parameter. *Ann Allergy Asthma Immunol* 2006;97:s1–s38.
- Perales B, Beltrani V, Bielory L. Dermatologic and allergic conditions of the eyelid. *Immunol Allergy Clin North Am* 2008;28(1):137–168.

9. Herbst RA, Uter W, Pirkwer C, et al. Allergic and non allergic periorbital dermatitis: patch test results of the information network of the departments of dermatology during a 5 year period. *Contact Dermatitis* 2004; 51:13–19.
10. Seitz CS, Bröcker EB, Trautmann A. Eyelid dermatitis due to sodium metabisulfite. *Contact Dermatitis* 2006;55(4):249–250.
11. Teixeira M, de Wachter L, Ronsyn E, et al. Contact allergy to para-phenylenediamine in a permanent eyelash dye. *Contact Dermatitis* 2006; 55(2):92–94.
12. -Dejobert Y, Delaporte E, Piette F, et al. Eyelid dermatitis with positive patch test to coconut diethanolamide. *Contact Dermatitis* 2005; 52(3):173.
13. Vaswani SK, Collins DD, Pass CJ. Severe allergic contact eyelid dermatitis caused by swimming goggles. *Ann Allergy Asthma Immunol* 2003;90(6): 672–673.
14. Jacob SE, Stechschulte S. Formaldehyde, aspartame and migraines—a possible connection. *Dermatitis* 2008;19(3):E10–E11.
15. Amin KA, Belsito DV. The aetiology of eyelid dermatitis: a 10-year retrospective analysis. *Contact Dermatitis* 2006;55(5):280–285.
16. Jacob SE, Burk CJ, Connelly EA. Patch testing: another steroid-sparing agent to consider in children. *Pediatr Dermatol* 2008;25(1):81–87.
17. Zemba C, Romaguera C, Vilaplana J. Allergic contact dermatitis from nickel in an eye pencil. *Contact Dermatitis* 1992;27:116.
18. Brandrup F. Nickel eyelid dermatitis from an eyelash curler. *Contact Dermatitis* 1991;25:77.
19. van Ketel WG, Bruynzeel DP. Allergic contact dermatitis from nickel in eyeshadow. *Contact Dermatitis* 1989;21(5):355.
20. Goh CL, Ng SK, Kwok SF. Allergic contact dermatitis from nickel in eyeshadow. *Contact Dermatitis* 1989;20(5):380–381.
21. Rietschel R, Fowler JF. *Fisher's Contact Dermatitis* 6. Hamilton, Ontario, Canada: BC Decker Inc; 2008:176, 417–418, 714.
22. Cooper S, Shaw S. Eyelid dermatitis: an evaluation of 232 patch test patients over 5 years. *Contact Dermatitis* 2000;42:291–293.
23. Malvestio A, Bovenzi M, Hoteit M, et al. *p*-Phenylenediamine sensitization and occupation. *Contact Dermatitis* 2011;64(1):37–42.
24. Li LF. A study of the sensitization rate to cocamidopropyl betaine in patients patch tested in a university hospital of Beijing. *Contact Dermatitis* 2008;58(1):24–27.
25. Hillen U, Grabbe S, Utter W. Patch test results in patients with scalp dermatitis: analysis of data of the Information Network of Departments of Dermatology. *Contact Dermatitis* 2007;56(2):87–93.
26. Militello G. Contact and primary irritant dermatitis of the nail unit diagnosis and treatment. *Dermatol Ther* 2007;20(1):47–53.
27. Hausen BM, Milbrodt M, Koenig WA. The allergens of nail polish. (I). Allergenic constituents of common nail polish and toluenesulfonamide-formaldehyde resin (TS-FR). *Contact Dermatitis* 1995;33(3):157–164.
28. Giorgini S, Bruci C, Francalanci S, et al. Prevention of allergic contact dermatitis from nail varnishes and hardeners. *Contact Dermatitis* 1994;31(5): 325–326.
29. Betts CJ, Dearman RJ, Heylings JR, et al. Skin sensitization potency of methyl methacrylate in the local lymph node assay: comparisons with guinea-pig data and human experience. *Contact Dermatitis* 2006;55(3): 140–147.
30. Nedorost S, Wagman A. Positive patch-test reactions to gold: patients' perception of relevance and the role of titanium dioxide in cosmetics. *Dermatitis* 2005;16(2):67–70.
31. Ehrlich A, Belsito DV. Allergic contact dermatitis to gold. *Cutis* 2000;65: 323–326.
32. Jacob SE, Brod B, Crawford GH. Clinically relevant patch test reactions in children—a United States based study. *Pediatr Dermatol* 2008;25(5): 520–527.
33. Valsecchi R, Imberti G, Martino D, et al. Eyelid dermatitis: an evaluation of 150 patients. *Contact Dermatitis* 1992;27:143–147.
34. Garcia-Melagres ML, de la Cuadra J, Martin B, et al. Sensitization to gallates: review of 46 cases. *Actas Dermosifiliogr* 2007;98(10):688–693.
35. Pinola A, Estlander T, Jolanki R, et al. Occupational allergic contact dermatitis due to coconut diethanolamide (cocamide DEA). *Contact Dermatitis* 1993;29(5):262–265.
36. Fowler JF Jr. Allergy to cocamide DEA. *Am J Contact Dermatitis* 1998;9(1):40–41.