
Eyelid dermatitis in patients referred for patch testing: Retrospective analysis of North American Contact Dermatitis Group data, 1994-2016



Erin M. Warshaw, MD, MS,^{a,b,c} Lindsey M. Voller, BA,^{a,c,d} Howard I. Maibach, MD,^e Kathryn A. Zug, MD,^f Joel G. DeKoven, MD,^g Amber R. Atwater, MD,^h Margo J. Reeder, MD,ⁱ Denis Sasseville, MD,^j James S. Taylor, MD,^k Joseph F. Fowler, Jr, MD,^l Melanie D. Pratt, MD,^m Jonathan I. Silverberg, MD,ⁿ Anthony F. Fransway, MD,^o Matthew J. Zirwas, MD,^p Donald V. Belsito, MD,^q James G. Marks, Jr, MD,^r and Vincent A. DeLeo, MD^s

Minneapolis, Minnesota; San Francisco and Los Angeles, California; Lebanon, New Hampshire; Toronto and Ottawa, Ontario, and Montreal, Quebec, Canada; Durham, North Carolina; Madison, Wisconsin; Cleveland, Columbus, and Cincinnati, Ohio; Louisville, Kentucky; Washington, District of Columbia; Fort Myers, Florida; and New York, New York

Background: Eyelid dermatitis is a common dermatologic complaint.

Objective: To characterize patients with eyelid dermatitis.

Methods: Retrospective analysis (1994-2016) of North American Contact Dermatitis Group data.

Results: Of 50,795 patients, 2332 (4.6%) had eyelid dermatitis only, whereas 1623 (3.2%) also had dermatitis of the eyelids and head or neck. Compared with patients without eyelid involvement ($n = 26,130$), groups with eyelid dermatitis only and dermatitis of the eyelid and head or neck were significantly more likely to be female, white, and older than 40 years, and to have a history of hay fever, atopic dermatitis, or both ($P < .01$). Final primary diagnoses included allergic contact dermatitis (eyelid dermatitis only: 43.4%; dermatitis of the eyelid and head or neck: 53.5%), irritant contact dermatitis (eyelid dermatitis only: 17.0%; dermatitis of the eyelid and head or neck: 9.8%), and atopic dermatitis

From the Department of Dermatology, Park Nicollet Health Services, Minneapolis^a; Department of Dermatology, University of Minnesota, Minneapolis^b; Department of Dermatology, Minneapolis Veterans Affairs Medical Center^c; University of Minnesota Medical School, Minneapolis^d; Department of Dermatology, University of California—San Francisco^e; Department of Dermatology, Dartmouth-Hitchcock Medical Center, Lebanon^f; Division of Dermatology, Sunnybrook Health Sciences Centre, University of Toronto, Ontario^g; Department of Dermatology, Duke University Medical Center, Durham^h; Department of Dermatology, University of Wisconsin School of Medicine and Public Health, Madisonⁱ; Division of Dermatology, Royal Victoria Hospital, McGill University, Montreal, Quebec^j; Department of Dermatology, Cleveland Clinic^k; Division of Dermatology University of Louisville^l; Division of Dermatology, University of Ottawa, Ontario^m; Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washingtonⁿ; Associates in Dermatology, Fort Myers^o; Department of Dermatology, Ohio State University, Columbus^p; Department of Dermatology, Columbia University, New York^q; Department of Dermatology, Pennsylvania State University, Hershey, Pennsylvania^r; and

Department of Dermatology, Keck School of Medicine, Los Angeles, California.^s

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Correspondence to: Lindsey M. Voller, BA, Park Nicollet Contact Dermatitis Clinic, 7550 34th Ave S, Ste 101, Minneapolis, MN 55450. E-mail: volle025@umn.edu.

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(eyelid dermatitis only: 13.1%; dermatitis of the eyelid and head or neck: 13.8%). Top 5 currently relevant allergens included nickel sulfate (eyelid dermatitis only: 18.6%; dermatitis of the eyelid and head or neck: 22.5%), fragrance mix I (eyelid dermatitis only: 16.5%; dermatitis of the eyelid and head or neck: 18.3%), methylisothiazolinone (eyelid dermatitis only: 16.5%; dermatitis of the eyelid and head or neck: 17.7%), gold sodium thiosulfate (eyelid dermatitis only: 14.7%; dermatitis of the eyelid and head or neck: 11.4%), and balsam of Peru (eyelid dermatitis only: 11.9%; dermatitis of the eyelid and head or neck: 12.6%). Both eyelid-involvement groups were significantly more likely to react to gold sodium thiosulfate, carmine, shellac, dimethylaminopropylamine, oleamidopropyl dimethylamine, and thimerosal ($P < .05$) compared with the no eyelid involvement group.

Limitations: Lack of specific distribution patterns of eyelid dermatitis and no long-term follow-up data.

Conclusion: Patch testing remains a critical tool in evaluating patients with eyelid dermatitis. (J Am Acad Dermatol 2021;84:953-64.)

Key words: allergic contact dermatitis; contact allergy; eyelid dermatitis; eyelids; irritant contact dermatitis.

INTRODUCTION

Eyelid dermatitis, a common dermatologic complaint, includes eczematous conditions and dermatoses (Table I).⁶⁻⁸ Eyelids are particularly susceptible to contact dermatitis, given thin delicate skin, occluded upper surface, hydrated stratum corneum facilitating penetration, and routine contact with allergens and irritants.⁹⁻¹¹ Common culprits include airborne substances (eg, fragrances), direct contactants (eg, cosmetics, ophthalmic medications), and ectopic exposures (eg, nail polish).¹ Surrounding areas, including the forehead, cheeks, and neck, are often also involved.^{1,11-13}

Reports have previously described patients with eyelid contact dermatitis (Table II). The 2 largest studies were from Europe (Germany and Austria⁸: N = 1641; Germany, Austria, and Switzerland⁶: N = 4779); common allergens included nickel, preservatives, fragrances, and neomycin. Smaller studies reported similar results.^{14,17-19} Most affected individuals were female patients, presumably because of use of cosmetic and fragrant products.^{7,16,19,20}

This study describes a large North American cohort with eyelid dermatitis referred for patch testing. We sought to determine the final diagnoses, frequency of currently relevant allergens with positive patch test results, relevant allergen sources, and relevant contributing irritants.

CAPSULE SUMMARY

- Eyelids are particularly susceptible to developing contact dermatitis; important allergens and irritants include metals, fragrances, preservatives, and medicaments.
- In our cohort, irritant contact dermatitis was more common when the eyelids were affected exclusively; allergic contact dermatitis predominated when head and neck sites were additionally involved. Atopic dermatitis was an important diagnosis among both groups.

METHODS

North American Contact Dermatitis Group database

This retrospective study involving deidentified North American Contact Dermatitis Group (NACDG) data was approved by the Minneapolis Veterans Affairs Medical Center's Subcommittee on Human Studies. Patch testing was conducted in accordance with NACDG standards.²¹ Collected data included patient demographics (age, sex, race, and occupation), history of atopy (asthma, atopic dermatitis, and hay fever), body site(s) of dermatitis, and final diagnoses.

Tested allergens varied by 2-year cycles; not all allergens were tested during every cycle. Current clinical relevance comprised reactions coded as "definite" (positive patch test or use test result with a skin contactant verified to contain the allergen), "probable" (allergen verified in skin contactant with a consistent clinical presentation), or "possible" (skin contactant possibly contained the allergen). Other relevance categories included "past" or "unknown." For each positive allergen result, the most likely exposure source was coded. Sources were also documented for positive relevant non-NACDG allergen results (additional allergens not part of the screening series); however, names of those allergens were not recorded.

An assessment of irritant contact dermatitis (ICD) based on clinical history and physical examination was also coded for each patient. If currently relevant ICD was present, the source was documented.

Abbreviation used:

NACDG: North American Contact Dermatitis Group

Study population

Patients patch tested by the NACDG (1994-2016) were included in this study. Three major subgroups were identified according to body site(s) of dermatitis (Fig 1): patients with eyelid involvement only, those with eyelid and head or neck involvement, and those without eyelid involvement. The no eyelid involvement group included individuals lacking eyelid involvement; patients were excluded from this group if “face not otherwise specified” or “scattered/generalized” was coded because these individuals may have had eyelid involvement that was not specifically coded as a separate site. This study included previously published data on eyelid dermatitis from the 2003-2004 NACDG cycle (n = 5145),¹⁵ as well as 117 patients from a separate 2006 analysis.⁷

Data analysis

Data were entered at a centralized location (Access 2010 [Microsoft Corporation, Redmond, WA] and Excel 2019 [Microsoft Corporation]). Demographics, allergens, and exposure sources are presented with descriptive analyses and 2-sided χ^2 tests (GraphPad Prism, version 8.2.1 for MacOS X, La Jolla, CA) with $P < .05$ considered statistically significant. There were no adjustments for multiple comparisons.

RESULTS

Eyelid involvement only

Of 50,795 patch-tested individuals, 4989 (9.8%) had “eyelid” coded as 1 of up to 3 sites of dermatitis; 2332 (4.6%) had eyelid involvement only (Fig 1). Compared with those without eyelid involvement (n = 26,130), patients with eyelid dermatitis only were significantly more likely to be female. Small differences were observed in patients who were white and older than 40 years; eyelid dermatitis only patients were more likely to report a history of either hay fever or atopic dermatitis (Table III). Individuals in the eyelid dermatitis only group had significantly higher frequencies of a final primary diagnosis of atopic dermatitis and seborrheic dermatitis and were slightly more likely to have ICD than individuals in the no eyelid involvement group. Eyelid dermatitis only patients were significantly less likely to have an occupationally-related skin condition.

Among the 1145 patients in the eyelid dermatitis only group who had a currently relevant reaction, 813 (71.0%) had NACDG screening allergen(s) only, 127 (11.1%) had non-NACDG allergen(s) only, and 205 (17.9%) had both. The top 5 NACDG allergens for eyelid dermatitis only patients included nickel sulfate (18.6%), fragrance mix I (16.5%), methylisothiazolinone (16.5%), gold sodium thiosulfate (14.7%), and balsam of Peru (11.9%) (Table IV). Of the 20 most common allergens, those that were significantly more frequent in the eyelid dermatitis only group compared with the no eyelid involvement group included gold sodium thiosulfate, neomycin, carmine, shellac, dimethylaminopropylamine, oleamidopropyl dimethylamine, and thimerosal. Allergens that were significantly less frequent included balsam of Peru, quaternium-15, cobalt chloride, bacitracin, and thiuram mix.

Eyelid and head or neck involvement

Of 1623 individuals with dermatitis of the eyelid and head or neck, eyelids were the primary site in 61.8%, followed by face not otherwise specified (26.4%), lips (4.9%), eyes (2.6%), scalp (2.2%), neck (1.6%), ears (0.4%), and nose (0.1%). Demographics of groups with dermatitis of the eyelid and head or neck versus no eyelid involvement were similar to those of the eyelid dermatitis only group, with few notable differences (Table III). Patients with dermatitis of the eyelid and head or neck were significantly more likely than those with either no eyelid involvement or eyelid dermatitis only to have a final primary diagnosis of allergic contact dermatitis (ACD) and significantly less likely to have a final primary diagnosis of ICD.

Among 983 patients with dermatitis of the eyelid and head or neck who had a currently relevant patch test allergen, 656 (66.7%) had NACDG screening allergen(s) only, 91 (9.3%) had non-NACDG allergen(s) only, and 236 (24.0%) had both. Patients with dermatitis of the eyelid and head or neck reacted to the same top 5 allergens as the eyelid dermatitis only group. Compared with patients with no eyelid involvement, those with dermatitis of the eyelid and head or neck were significantly more likely to have currently relevant reactions to nickel sulfate, gold sodium thiosulfate, carmine, shellac, dimethylaminopropylamine, oleamidopropyl dimethylamine, and thimerosal. Allergens that were significantly less frequently positive in the group with dermatitis of the eyelid and head or neck included quaternium-15 and bacitracin.

Table I. Differential diagnosis of eyelid dermatitis¹⁻⁵

Diagnosis	Description	Eyelid/periorbital signs and symptoms
Allergic contact dermatitis	Delayed (type IV) hypersensitivity reaction	Erythema, papules/pustules, scaling, lichenification, pruritus > burning/stinging
Atopic dermatitis	Local manifestation of systemic atopy; often associated with hay fever, asthma, or both	Periorbital hyperpigmentation, cracking/scaling, erythema, Dennie-Morgan lines, lichenification, pruritus
Blepharitis	Inflammation of eyelid margins (eyelashes, sebaceous glands, or meibomian glands)	Burning/stinging, crusting/scaling, debris, erythema, edema, pruritus
Irritant contact dermatitis	Direct cell damage after contact with irritant	Burning/stinging > pruritus, cracking/scaling, erythema
Seborrheic dermatitis	Papulosquamous disorder affecting sebum-rich areas	Crusting, erythema, flaky/greasy debris of eyebrows > eyelids
Contact urticaria	Immediate (type I) hypersensitivity reaction	Burning, edema, erythema, pruritus, urticaria
Systemic contact dermatitis	Delayed (type IV) hypersensitivity reaction	Rarely, localized refractory eyelid dermatitis may be present, although dyshidrotic hand dermatitis and intertriginous/flexural exanthema are better-known patterns
Infections	Viral, bacterial, fungal infections	Varies with causative organism
Ocular rosacea	Form of rosacea often associated with blepharitis and hyperemia; can be initial manifestation of rosacea	Burning, dryness, debris, erythema, foreign-body sensation, irritation, photophobia
Periorbital cellulitis	Acute infection of periorbital skin and deep tissues	Unilateral erythema, edema, warmth, fever, pain, malaise
Angioedema	IgE-mediated allergic reaction or bradykinin-induced nonallergic reaction causing swelling of the periorbital region	Nonpitting periorbital edema without pruritus or overlying epidermal changes
Thyroid ophthalmopathy	Autoimmune inflammatory condition classically associated with Graves disease	Eyelid retraction, exophthalmos, optic nerve dysfunction, extraocular muscle involvement
Psoriasis	Eyelid with/without eyebrow involvement and typical psoriatic plaques	Well-defined salmon-colored plaques with overlying silvery scale
Dermatomyositis	Inflammatory myopathy with characteristic cutaneous findings	Heliotrope rash (violaceous periorbital erythema)
Skin cancer	Neoplastic lesion most commonly originating on lower eyelid	Typically unilateral, rapid growth, spontaneous bleeding or ulceration
Sjögren syndrome/dry eyes	Decreased tear formation	Eyelid dermatitis may occur, likely secondary to rubbing

IgE, Immunoglobulin E.

Allergen sources

Personal care products were the most common source for 6 of the top 10 NACDG allergens (Supplemental Table I available via Mendeley at <https://data.mendeley.com/datasets/wbckkkrygp/1>). The remaining allergens were most frequently associated with jewelry, hair products, and topical antibiotics. Sources for supplemental, non-NACDG allergens were similar.

Currently relevant irritant contact dermatitis sources

Two hundred forty-five patients with eyelid dermatitis only and 138 with dermatitis of the eyelid

and head or neck were considered to have relevant environmental irritants; an additional 135 with eyelid dermatitis only and 113 with dermatitis of the eyelid and head or neck had both ACD and ICD. Personal care products predominated as irritant sources for both groups (Supplemental Table I). Medicaments, cleansers, hair products, and “persons” (perspiration, saliva, and tears) were also common.

DISCUSSION

This 22-year analysis of a large North American cohort yielded several important findings. Individuals with eyelid dermatitis were primarily females and had a final diagnosis of ACD, ICD,

Table II. Select literature describing patch test results among patients with eyelid dermatitis

Study	Study population, no. of patients	Frequency of eyelid dermatitis, no. of patients (% of total)	Most common allergens	Clinical relevance	Comments
Valsecchi et al, ¹⁴ Italy, 1990-1991	1158 general patch test patients	Eyelid dermatitis: 150 (13.0%) Female*: 135 (90%) Exclusively eyelids: 54 (36.0%) Eyelids + face: 49 (32.7%)	Nickel sulfate: 42.0% Kathon Cosmetic Grade (MCI/MI): 10.0% Fragrance mix: 8.0% Diaminodiphenylmethane: 7.4% Thimerosal: 6.7%	Clinical relevance not specifically investigated, although commented that nickel was unable to be established as relevant in any positive cases	Female patients with eyelid dermatitis significantly more likely to react to Kathon Cosmetic Grade than those without eyelid dermatitis
Amin and Belsito, ⁷ United States, 1994-2004 [†]	1215 general patch test patients	Eyelid dermatitis: 105 (8.6%) Female*: 93 (88.6%) Exclusively eyelids: 54 (51.4%) Eyelids + face: 23 (21.9%)	Fragrance mix/other fragrances: 28.3% Nickel sulfate: 13.0% Neomycin/aminoglycosides: 10.9% Oleamidopropyl dimethylamine: 10.9% Benzalkonium chloride: 8.7%	Only currently clinically relevant reactions included when analyzing allergens	Seborrheic dermatitis most common diagnosis among patients with eyelid dermatitis only (46.3%)
Herbst et al, ⁸ Germany and Austria, 1995-1999	49,256 general patch test patients	Allergic periorbital contact dermatitis: 1053 (2.1%) Nonallergic periorbital dermatitis: 588 (1.2%) Female*: 80.3%	Nickel sulfate: 17.8% Thimerosal: 10.2% Fragrance mix: 9.4% Neomycin B: 9.3% Phenylmercuric acetate: 9.2%	Clinical relevance not specifically investigated	Patch testing with personal care products or medications revealed the relevant allergen among a greater number of cases compared with controls (2.9% vs 1.6%)
Landeck et al, ⁶ Germany, Austria, Switzerland, 2001-2010	101,403 general patch test patients	Periorbital dermatitis: 4779 (4.7%) ACD: 1529 (32.0%) Atopic dermatitis: 793 (16.6%) Female*: 3874 (81.1%)	Nickel sulfate: 17.5% Toluene 2,5-diamine: 10.6% Thimerosal: 9.3% Phenylmercuric acetate: 8.3% Balsam of Tolu: 7.9%	Clinical relevance not specifically investigated	Among patients referred for suspected contact allergy to ophthalmic medications, increased rates of sensitization to phenylmercuric acetate, antibiotics, and phenylephrine-HCl observed
Rietschel et al, ¹⁵ United States and Canada, 2003-2004*	5145 general patch test patients	Eyelid dermatitis only and final diagnosis of ACD: 268 (5.2%)	Gold sodium thiosulfate: 8.2% Fragrance mix: 7.1% Balsam of Peru: 6.3% Nickel sulfate: 6.0% Neomycin: 3.3%	Inclusion criteria included patients with reactions of current clinical relevance	42.4% of sources attributed to cosmetics and beauty products
Herro et al, ¹⁶ United States, 2004-2007	204 patients with eyelid-only dermatitis	Eyelid dermatitis only and final diagnosis of ACD: 31 (15.2%) Female*: 23 (74.2%)	Formaldehyde: 35.5% Nickel sulfate: 25.8% Balsam of Peru: 22.6% Fragrance mix I: 19.4% Bronopol: 19.4%	Inclusion criteria included patients with reactions of current clinical relevance	On formaldehyde avoidance, 90% of formaldehyde-sensitive patients experienced full remission of symptoms

Continued

Table II. Cont'd

Study	Study population, no. of patients	Frequency of eyelid dermatitis, no. of patients (% of total)	Most common allergens	Clinical relevance	Comments
Wenk and Ehrlich, ¹⁷ United States, 2006–2010	100 patients with eyelid dermatitis tested to North American standard and fragrance series	88 (88.0%) tested positive to at least 1 relevant allergen on standard and/or fragrance trays	Fragrance mix II: 19% Fragrance mix I: 17% Balsam of Peru: 17% Nickel sulfate: 15% Cinnamic alcohol: 15%	Only currently clinically relevant reactions included when analyzing allergens	36% of fragrance allergens would have been missed had specific fragrance series testing not been performed
Crouse et al, ¹⁸ United States, 2008–2015	268 general patch test patients	Eye lid dermatitis: 68 (22.1%) Exclusively eyelids: 22.0% Eyelids + head/neck: 30.9%	Gold: 17.5% Nickel: 15.0% Balsam of Peru: 12.5% Bacitracin: 10.0%	Only currently clinically relevant reactions included when analyzing allergens	Allergic contact dermatitis was the only diagnosis in patients with unilateral eyelid symptoms
Assier et al, ¹⁹ France, 2014–2016	264 patients with eyelid dermatitis	Exclusively eyelids: 110 (41.6%) Female*: 238 (90.2%)	Methylisothiazolinone: 10.2% Fragrance mix I: 3.0% Nickel sulfate: 2.7% Linalool: 2.7% Limonene: 2.3%	Inclusion criteria included patients with reactions of current clinical relevance	All 4 eyelids (bilateral upper and lower) involved in 75.6% of cases

*Female percentage is number of females in the eyelid patient population only.

†One hundred seventeen patients in this study also included in current study.

or atopic dermatitis at a higher frequency than individuals without eyelid involvement. ACD was significantly more common in dermatitis of the eyelid and head or neck, whereas ICD was significantly more common in eyelid dermatitis only. The top 5 NACDG currently relevant allergens included nickel sulfate, fragrance mix I, methylisothiazolinone, gold sodium thiosulfate, and balsam of Peru. In addition, both eyelid dermatitis only and dermatitis of the eyelid and head or neck groups were significantly more likely than the no eyelid involvement group to react to gold sodium thiosulfate, specific makeup chemicals (carmine and shellac), surfactants (dimethylaminopropylamine and oleamidopropyl dimethylamine), and an eyedrops preservative (thimerosal). Finally, allergen and irritant sources commonly originated from personal care products, hair products, jewelry, and topical antibiotics.

Patient demographics

The eyelid dermatitis patients in our study population were predominantly female, and multiple previous investigations have noted similar findings.^{8,14,20,22-24} This sex distribution is likely secondary to increased usage of cosmetic products by females. The usage of facial products by males is increasing, so future trends may differ.²⁵

ACD was the most common primary diagnosis for both eyelid dermatitis only and dermatitis of the eyelid and head or neck, but the proportion of patients with ACD was significantly higher for dermatitis of the eyelid and head or neck (53.5%) compared with either eyelid dermatitis only (43.4%) or no eyelid involvement (46.3%). This is a helpful clinical finding that is also logical; allergens commonly migrate to surrounding areas even when applied only to the eyes or eyelids. Similarly, allergens used on the scalp or face may disproportionately affect the eyelids because of thin skin and occlusion.

ICD, atopic dermatitis, and seborrheic dermatitis were also common. ICD was significantly more common in eyelid dermatitis only compared with either dermatitis of the eyelid and head or neck or no eyelid involvement. This is another helpful and logical clinical finding. ICD depends on skin barrier function; the thin eyelid skin, combined with an occluded upper surface, can lead to irritation, whereas thicker unoccluded primary sites remain unaffected.²⁶ Groups with eyelid dermatitis only and dermatitis of the eyelid and head or neck had significantly higher frequency of self-reported atopic dermatitis, as well as a final primary diagnosis of atopic dermatitis, compared with the no eyelid involvement group. Eyelids are often affected in

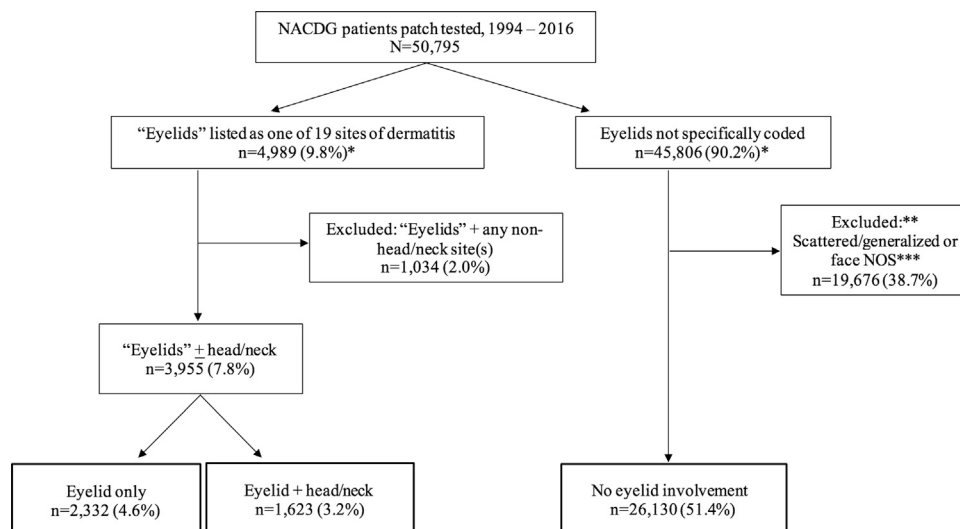


Fig 1. Study population flow diagram. *All percentages are of total number of patients tested (N = 50,795). **Because of the difficulty in assigning relevance to a body location, patients were excluded from the eyelids groups if they had eyelid dermatitis in addition to involvement of a non-head/neck body site (eg, eyelid + trunk with textile dye positive result; not possible to confidently associate the allergen with eyelid/head/neck location because the trunk was also involved). Similarly, patients were excluded from the no eyelid involvement group if their dermatitis site was coded as “face not otherwise specified” or “scattered/generalized” because these individuals may have had eyelid involvement that was not specifically coded as a separate site. *NACDG*, North American Contact Dermatitis Group; ****NOS*, not otherwise specified.

atopic dermatitis, possibly because of environmental airborne exposures and chronic rubbing or scratching behaviors.² Although dust mite contact reactions may also contribute, our group does not routinely test for these fomites.

We also demonstrated significantly higher frequency of seborrheic dermatitis, consistent with seborrheic patterns of scalp and periorcular or eyebrow involvement. Seborrheic dermatitis has previously been described as a possible trigger for eyelid atopic dermatitis.²⁷

Clinically relevant allergens and associated sources

Metals. Consistent with some previous reports, nickel sulfate was the leading allergen in our eyelid-involvement groups.^{6,8,10,14} Other studies have found gold,^{15,18} fragrance components,^{7,17} or preservatives^{16,19} as top allergens. In our study, jewelry accounted for most nickel sources, followed by miscellaneous consumer items and personal grooming devices and applicators. The majority of jewelry sources likely explain why nickel reactions were significantly higher among patients with dermatitis of the eyelid and head or neck compared with no eyelid involvement (but nonsignificant for eyelid dermatitis only), considering that the neck and ears were included in dermatitis of the eyelid and head or neck. Nickel has also been reported to cause eyelid

ACD from contact with eyeshadows, eyeliners, eyelash curlers, and eyeglass frames.²⁸⁻³¹ Anecdotally, approximately half of eyelash curlers tested by our group have released nickel and many patients' disease clears with avoidance of this source. Hand-transfer contact dermatitis may also occur because sweat from fingers can leach nickel from metallic objects; this phenomenon has occurred with operating room equipment, and eyelid dermatitis specifically has resulted from the use of metal nail files.^{27,32,33}

Gold, a well-known contact sensitizer and a recognized cause of eyelid ACD, demonstrated statistically higher frequencies of reactions among both eyelid-involvement groups compared with the no eyelid involvement group. ACD to gold typically presents as either dermatitis in the site of contact with gold jewelry (eg, fingers, earlobes) or as eyelid, face, or neck dermatitis resulting from transfer from the hands.^{34,35} Ectopic transfer is theorized to occur from the use of cosmetics and inorganic sunscreen containing titanium dioxide, which can adsorb gold ions on the face and eyelids.^{36,37} The previous 2003-2004 *NACDG* study found that gold was the most common allergen for patients with eyelid-only dermatitis (8.2%).¹⁵ In the present study, gold was tested only from 1996 to 2004; 14.7% of patients with eyelid dermatitis only and 11.4% of those with dermatitis of the eyelid and head or neck had currently clinically

Table III. Patient demographics*

Demographics	Eyelid dermatitis only, no. (%)	Dermatitis of eyelids + head/neck, [†] no. (%)	No eyelid dermatitis, [‡] no. (%)	Eyelid dermatitis only vs no eyelid dermatitis		Dermatitis of eyelids + head/neck vs no eyelid dermatitis	
				P value	RR (95% CI)	P value	RR (95% CI)
Total patients	2332	1623	26,130				
Sex							
Female	2062 (88.4)	1486 (91.6)	16,032 (61.4)	<.001	1.44 (1.42-1.47)	<.001	1.49 (1.47-1.52)
Age, y							
Mean	48.0	48.6	47.4				
>40	1596 (68.4)	1156 (71.3)	17,033 (65.2)	.002	1.05 (1.02-1.08)	<.001	1.09 (1.06-1.13)
Race							
White	2096 (90.3)	1440 (89.3)	22,621 (87.0)	<.001	1.04 (1.02-1.05)	.007	1.03 (1.01-1.04)
Atopy history							
Hay fever	736 (31.7)	516 (31.9)	6613 (25.4)	<.001	1.25 (1.17-1.33)	<.001	1.26 (1.17-1.35)
Atopic dermatitis [§]	486 (20.9)	412 (25.5)	4719 (18.1)	<.001	1.15 (1.06-1.25)	<.001	1.41 (1.29-1.53)
Asthma	296 (12.7)	221 (13.7)	3460 (13.3)	.46	0.96 (0.86-1.07)	.66	1.03 (0.91-1.17)
Primary diagnosis							
Allergic contact dermatitis	1012 (43.4)	865 (53.5)	12,046 (46.3)	.009	0.94 (0.89-0.98)	<.001	1.16 (1.10-1.21)
Irritant contact dermatitis	396 (17.0)	159 (9.8)	3752 (14.4)	<.001	1.18 (1.07-1.30)	<.001	0.68 (0.59-0.79)
Other dermatitis	356 (15.3)	177 (10.9)	4825 (18.5)	.001	0.82 (0.75-0.91)	<.001	0.59 (0.51-0.68)
Atopic dermatitis	306 (13.1)	223 (13.8)	1790 (6.9)	<.001	1.91 (1.71-2.14)	<.001	2.01 (1.76-2.28)
Other diagnosis	155 (6.7)	122 (7.5)	3418 (13.1)	<.001	0.51 (0.43-0.59)	<.001	0.57 (0.48-0.68)
Seborrheic dermatitis	105 (4.5)	72 (4.5)	215 (0.8)	<.001	5.46 (4.34-6.86)	<.001	5.39 (4.15-7.00)
Occupationally related							
Yes	52 (2.2)	33 (2.0)	5105 (19.6)	<.001	0.11 (0.09-0.15)	<.001	0.10 (0.07-0.15)
No/unsure	2276 (97.8)	1584 (98.0)	20,993 (80.4)				

CI, Confidence interval.

*Denominators varied slightly because of available data.

[†]Patients with eyelid and head or neck involvement (eg, face not otherwise specified, lips, nose, eyes, ears, scalp, neck).

[‡]Excluded patients with scattered or generalized involvement or involvement of the face that was not otherwise specified (assuming these participants may have had eyelid involvement).

[§]Self-reported history of childhood flexural dermatitis.

^{||}Up to 3 diagnoses could be coded, but only the primary diagnosis is listed in the table.

relevant reactions. Positive patch test reactions to gold may have no clinical relevance; a 2- to 3-month trial of gold jewelry avoidance is needed to establish relevance.³⁵

Fragrances. Multiple fragrance allergens composed the top 20 allergens (fragrance mix I and II, balsam of Peru, and cinnamic aldehyde), consistent with results of previous studies.^{7,14,17} Eyelid dermatitis can result in fragrance-sensitive individuals from direct application of fragrance-containing products, as well as through airborne exposures (eg, essential oil aromatherapy, plant particles).³⁸ Some reports demonstrated substantially increased frequency of fragrance reactions for eyelid dermatitis compared with those without eyelid dermatitis,^{7,14} whereas other studies documented lower frequency.^{8,39} This discrepancy may be explained by the ubiquitous presence of fragrance in cosmetic products used on many body sites, leading to variable results compared with those for controls. Suspected fragrance allergy

in cases of eyelid dermatitis may warrant testing beyond the NACDG screening series; Wenk and Ehrlich¹⁷ found that 36% of fragrance markers would have been missed had supplementary fragrance series testing not been performed.

Preservatives. Methylisothiazolinone has caused an epidemic of ACD during the past decade.⁴⁰ It is often present in shampoos and conditioners—the most common source of methylisothiazolinone in our study—and ACD can present as eyelid dermatitis from runoff during hair washing.⁴¹ Additional reported sources of methylisothiazolinone-associated eyelid dermatitis have included false eyelash glue,⁴² eye cleansing lotion,⁴³ and makeup remover wipes.⁴⁴ The high frequency of methylisothiazolinone allergy in our study parallels the trends demonstrated during the past 2 NACDG testing cycles. Since methylisothiazolinone was added to the NACDG screening series in 2013, frequency has increased from 10.9% (2013-2014) to 13.4% (2015-2016).⁴⁵

Table IV. Top 20 currently relevant allergens in study subgroups

Allergen	Eyelid dermatitis only			Eyelid + head/neck dermatitis			No eyelid dermatitis			Eyelid dermatitis only vs no eyelid dermatitis		Eyelid + head/neck dermatitis vs no eyelid dermatitis	
	No. of patients tested*	Clinically relevant reaction, no. (%)	Rank order	No. of patients tested*	Clinically relevant reaction, no. (%)	Rank order	No. of patients tested*	Clinically relevant reaction, no. (%)	Rank order	P value	RR (95% CI)	P value	RR (95% CI)
Nickel sulfate, 2.5% pet	1137	211 (18.56)	1	968	218 (22.52)	1	13,840	2395 (17.30)	1	.28	1.07 (0.94-1.22)	<.001	1.30 (1.15-1.47)
Fragrance mix I, 8.0% pet	1145	189 (16.51)	2	983	180 (18.31)	2	14,010	2239 (15.98)	3	.64	1.03 (0.90-1.18)	.055	1.15 (0.99-1.31)
MI, 0.2% aq	309	51 (16.50)	3	282	50 (17.73)	3	2788	477 (17.11)	2	.79	0.96 (0.74-1.25)	.79	1.04 (0.79-1.34)
Gold sodium thiosulfate, 0.5% pet	360	53 (14.72)	4	281	32 (11.39)	5	5679	338 (5.95)	15	<.001	2.47 (1.88-3.22)	<.001	1.91 (1.35-2.67)
Balsam of Peru (<i>Myroxylon pereirae</i>), 25.0% pet	1142	136 (11.91)	5	974	123 (12.63)	4	13,871	2065 (14.89)	4	.006	0.80 (0.68-0.94)	.055	0.85 (0.71-1.00)
Formaldehyde, 2.0% aq	309	27 (8.74)	6	283	19 (6.71)	8	2789	285 (10.22)	7	.41	0.86 (0.59-1.24)	.06	0.66 (0.42-1.02)
Neomycin, 20.0% pet	1142	93 (8.14)	7	973	53 (5.45)	15	13,853	861 (6.22)	14	.01	1.31 (1.07-1.61)	.34	0.88 (0.67-1.14)
Fragrance mix II, 14.0% pet	664	52 (7.83)	8	603	49 (8.13)	6	6405	451 (7.04)	9	.45	1.11 (0.84-1.46)	.32	1.15 (0.87-1.53)
Quaternium-15, 2.0% pet	1141	76 (6.66)	9	974	73 (7.49)	7	13,863	1667 (12.02)	5	<.001	0.55 (0.44-0.69)	<.001	0.62 (0.50-0.78)
Cinnamic aldehyde, 1.0% pet	1041	64 (6.15)	10	896	49 (5.47)	13	12,463	604 (4.85)	21	.06	1.27 (0.99-1.63)	.40	1.13 (0.85-1.49)
Carmine, 2.5% pet	109	6 (5.50)	11	154	10 (6.49)	9	1067	21 (1.97)	49	.02	2.80 (1.17-6.51)	<.001	3.30 (1.60-6.72)
Cobalt chloride, 1.0% pet	1144	58 (5.07)	12	982	60 (6.11)	10	14,011	978 (6.98)	10	.014	0.73 (0.56-0.94)	.30	0.88 (0.68-1.12)
Benzalkonium chloride, 0.1% aq	100	5 (5.00)	13	78	2 (2.56)	35	1403	30 (2.14)	44	.07	2.34 (0.95-5.62)	.80	1.20 (0.32-4.34)
Shellac, 20.0% aq	243	12 (4.94)	14	226	8 (3.54)	27	2159	21 (0.97)	81	<.001	5.08 (2.55-10.01)	<.001	3.64 (1.66-7.91)
Bacitracin, 20.0% pet	1142	56 (4.90)	15	981	47 (4.79)	20	14,019	977 (6.97)	11	.008	0.70 (0.54-0.91)	.009	0.69 (0.52-0.91)
DMAPA, 1.0% aq	552	27 (4.89)	16	509	31 (6.09)	11	4951	91 (1.84)	52	<.001	2.66 (1.75-4.03)	<.001	3.31 (2.23-4.90)
Oleamidopropyl dimethylamine, 0.1% aq	551	26 (4.72)	17	509	31 (6.09)	11	4949	140 (2.83)	36	.014	1.67 (1.11-2.50)	<.001	2.15 (1.47-3.13)
Thiuram mix, 1.0% pet	1142	53 (4.64)	18	973	41 (4.21)	24	13,864	937 (6.76)	12	.006	0.69 (0.52-0.90)	.002	0.62 (0.46-0.84)
Thimerosal, 0.1% pet	268	12 (4.48)	19	235	11 (4.68)	21	4918	95 (1.93)	50	.004	2.32 (1.29-4.11)	.004	2.42 (1.32-4.38)
MCI/MI, 0.01% aq	1145	50 (4.37)	20	981	44 (4.49)	22	13,995	801 (5.72)	16	.06	0.76 (0.58-1.01)	.104	0.78 (0.58-1.05)

DMAPA, Dimethylaminopropylamine; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone.

*Total number of patients with currently clinically relevant allergens, adjusted for the cycles in which the allergen was tested. Current clinical relevance was defined as definite (positive patch test or use test result with a skin contactant verified to contain the allergen), probable (allergen verified in skin contactant with a consistent clinical presentation), or possible (skin contactant possibly contained the allergen) (excludes past or unknown relevance). Denominator also includes patients with positive non-North American Contact Dermatitis Group allergen reactions.

Thimerosal is a mercury-containing preservative used in vaccines, and occasionally otic or ophthalmic products. A recent internet search found that it is still present in certain ophthalmic solutions. Although positive patch test results to thimerosal are common, current relevance is rare,⁴⁶ and it was removed from the NACDG screening series in 2003. The frequency decreased in the 2 eyelid-involvement groups from 1994 (15.8%) to 2002 (6.3%), likely because of decreased use.

Makeup-related chemicals. Patients with eyelid dermatitis only and those with dermatitis of the eyelid and head or neck were significantly more likely to react to shellac compared with patients with no eyelid involvement. Shellac is a natural resin derived from the *Kerria* (formerly *Laccifer* and then *Tachardia*) *lacca* insect.⁴⁷ Shellac in mascara is documented to cause eyelid ACD.⁴⁸⁻⁵⁰

Carmine, a red pigment obtained from the insect *Dactylopius coccus*,⁵¹ was found to be more common in both eyelid-involvement groups. ACD specifically affecting the eyelids⁵² and cheeks⁵³ has been described with use of carmine-containing cosmetics; however, type I hypersensitivity reactions are more commonly reported.⁵⁴ Anecdotal experience indicates that carmine is an irritant, so mild reactions (especially in atopic patients) should be interpreted with caution.

Surfactants. Both eyelid-involvement groups had significantly increased frequencies of reactions to dimethylaminopropylamine and oleamidopropyl dimethylamine compared with the no eyelid involvement group. Oleamidopropyl dimethylamine is a surfactant related to cocamidopropyl betaine, whereas dimethylaminopropylamine and amidoamine are impurities that may remain after the manufacturing of cocamidopropyl betaine. These surfactants represent an important source of eyelid dermatitis. Eyelid dermatitis secondary to dimethylaminopropylamine has been reported from shampoo⁵⁵ and eye makeup remover.⁵⁶ Additionally, a recent study analyzing male facial dermatitis found that the eyelids were affected in 23.5% of patients, and males with facial dermatitis were significantly more likely to have allergic reactions to dimethylaminopropylamine than male patients without facial dermatitis.²⁵

Non-NACDG allergens

Approximately 35% of patients with eyelid dermatitis only and those with dermatitis of the eyelid and head or neck reacted to both non-NACDG and NACDG allergens; of these, approximately 10% reacted to non-NACDG allergens alone. Personal care products, medicaments, jewelry, and hair

products represented common non-NACDG allergen sources. The relatively high frequency of medicament sources in particular has implications for patch testing; testing patients' products, especially eyedrops and ophthalmic medications, is important because the culprit is often the active ingredient.³ In cases of suspected ACD to ophthalmic agents with negative patch test results, adjuvant testing methods such as repeated open application testing are necessary because patch testing results with ophthalmic medications are often falsely negative. These methods, including tape stripping, are described elsewhere.^{3,57-59}

Relevant irritants

Relevant ICD was identified in 16.3% of patients with eyelid dermatitis only and 15.5% of those with dermatitis of the eyelid and head or neck. Personal care products were among the most frequent irritant sources for both eyelid-involvement groups. Given commonality among implicated sources, as well as similar clinical presentations, distinguishing eyelid ICD from ACD can be difficult. Pruritus may indicate ACD, whereas stinging or burning may suggest ICD.¹¹ Patch testing is valuable in differentiating these two.

LIMITATIONS

The NACDG database does not distinguish between specific eyelid patterns (eg, upper vs lower, unilateral vs bilateral). Names of non-NACDG allergens are not recorded (only sources of those allergens). NACDG allergens of past or unknown clinical relevance were excluded to ensure relationship with dermatitis of the eyelid and head or neck. Long-term follow-up data are lacking, so whether patients improved after allergen and irritant avoidance is unknown.

CONCLUSIONS

Eyelid contact dermatitis is a frequent dermatologic complaint. ICD was significantly more common in eyelid dermatitis only patients, whereas dermatitis of other body sites plus the eyelids was significantly associated with ACD. Eyelid ACD was commonly caused by metals and fragrances; methylisothiazolinone has emerged as an important allergen. Allergen and irritant sources primarily included personal care products, makeup, shampoos, jewelry, and topical antibiotics. Patch testing remains an important tool in the evaluation of patients with eyelid dermatitis.

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