

The aetiology of eyelid dermatitis: a 10-year retrospective analysis

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Few studies have examined the aetiology of eyelid dermatitis across broad demographics. The objectives of this study were (i) to compare the diagnoses of patients with isolated eyelid dermatitis to the diagnoses of patients with additional sites of involvement and (ii) to determine the relevant allergens among patients with allergic eyelid dermatitis. A retrospective analysis of 1215 patients patch tested over 10 years was conducted in this study. Compared to patients without eyelid dermatitis, patients with this entity were more often female. Of the 105 patients with eyelid dermatitis, 43.8% had allergic contact dermatitis (ACD), 36.2% seborrhoeic dermatitis, 11.4% other dermatitis/dermatoses, 7.6% irritant contact dermatitis, 3.8% psoriasis, and 2.9% atopic eczema. With isolated eyelid dermatitis, seborrhoeic dermatitis was the most frequent diagnosis (46.3%) followed by ACD (35.2%). Allergens commonly causing allergic eyelid dermatitis consisted of fragrances, metals, neomycin, oleamidopropyl dimethylamine, tosylamide formaldehyde resin, benzalkonium chloride, and other preservatives. When evaluated according to sites of involvement, seborrhoeic dermatitis was diagnosed most often in patients with isolated eyelid dermatitis, but when dermatitis was distributed to facial or other sites, ACD was the most frequent diagnosis. A majority of the causative allergens for eyelid dermatitis are not present on the Food and Drug Administration-approved panels available in the USA.

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Patients presenting with eyelid dermatitis are often a challenge to diagnose and treat despite an extensive history and physical examination. Potential causes include allergic contact dermatitis (ACD), irritant contact dermatitis, atopic dermatitis, seborrhoeic dermatitis, psoriasis, dermatomyositis, infections, rosacea, and others. Eyelid dermatitis may be the result of a combination of factors; for example, ACD superimposed on a primary non-allergic dermatitis such as atopic eczema or seborrhoeic dermatitis. It may also present as an iatrogenic complication of treatment for a different condition.

The eyelids are susceptible to ACD owing to their very thin skin (0.55 mm compared to other facial areas that are about 2.0 mm thick), which allows for easier penetration of both contact and airborne allergens (1). Therefore, although an allergen may come in contact with other body areas, the eyelids alone may manifest a reaction. Further obscuring the clinical presentation is the fact that ACD can exist 'ectopically' on the eyelids, with allergens spread beyond the primary site

of contact. A prime example of this is allergy to the resins in nail varnish. Besides autoinoculation, contact with others who transmit the allergens can result in what is known as 'consort' dermatitis (2).

Previous studies of patients with eyelid dermatitis have consistently shown ACD to be the most frequent cause. These reports have shown that 29–77% of all eyelid dermatitis cases were due to ACD (1–7). Valsecchi and colleagues evaluated 150 patients with eyelid dermatitis and found that allergic patch test reactions to nickel sulfate, methylchloroisothiazolinine/methylisothiazolinone, and fragrance mix occurred more frequently in these patients than in the control population (7). Ockenfels and colleagues analysed 609 patients, also with periorbital eczema, and determined the leading allergens to be aminoglycoside antibiotics (especially neomycin and gentamycin), other medicaments (e.g. phenylephrine), and preservatives (especially thimerosal) (5). Very few studies have investigated the aetiology of eyelid dermatitis based on isolated eyelid involvement compared to dermatitis concurrently affecting other areas.

In this 10-year retrospective analysis, we examined patients' records at a midwestern US centre to determine the most common causes of eyelid dermatitis and how the aetiology differed depending on the cutaneous sites involved. We also assessed the influence of age, sex, race, and atopic history on the aetiology of eyelid dermatitis. The objectives of this investigation were (i) to determine the final diagnosis(es) among patients with dermatitis affecting only the eyelids compared to those whose eyelid dermatitis was accompanied by cutaneous involvement in other sites, (ii) to identify the relevant allergens among patients determined to have ACD, and (iii) to elucidate the source(s) that may contain the more common allergens and consequently should be avoided.

Methods

Between 1 January 1994 and 31 December 2004, patch testing was performed by 1 of the authors (D. V. B.) on 1215 patients who presented with a clinical suspicion of ACD. Patients were first asked to complete a standardized questionnaire regarding demographic, medical, and occupational data. All patients were tested with the North American Contact Dermatitis Group's (NACDG's) standard screening tray, and most were tested with other relevant allergen trays based on information gleaned from the history, physical examination, and clinical suspicion.

Test allergens were purchased from Chemo-technique Diagnostics AB (Malmö, Sweden). Patients were patch tested using Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) applied to the upper back. After the initial application of

patches, patients returned for inspection and for determination of results after both 48 and 96 hr. Results were assessed according to the standard NACDG methodology (8). Reaction morphologies with scores of 1 (weak, nonvesicular, and indurated erythema), 2 (strong, oedematous or vesicular), and 3 (extreme, spreading, bullous, or ulcerative) were considered positive (8). Only relevance scores of 1 (definite), 2 (probable), and 3 (possible) were considered when determining the aetiological agents for ACD (8).

All data were recorded, retrieved, and evaluated using a computer database. Queries, calculations, and reports were made using Microsoft Access 2000 (Seattle, WA, USA). Statistical analysis was performed using the 2005 version of StatsDirect statistical software 2.4.5 (StatsDirect Ltd, Cheshire, UK) using the chi-square test and the Fischer's exact test when the chi-square test was deemed unreliable due to small expected values of <5%. A *P* value of 0.05 or less was considered to be statistically significant.

Results

Of the 1215 patients who underwent patch testing during this 10-year period, 751 (61.8%) were female and 464 (38.2%) male. The vast majority of the patients, 1037, were Caucasian (85.4%), and only 108 (8.9%), 29 (2.4%), 22 (1.8%), and 19 (1.6%) were African-American, Hispanic, Asian, and other ethnicities, respectively. Of these 1215 patients, 105 (8.6%) had eyelid dermatitis and were further analysed in this report.

As shown in Table 1, of the 105 patients with a suspected ACD of the eyelids, females (*n* = 93;

Table 1. Demographics of patients patch tested for suspected allergic eyelid dermatitis

	All eyelid, <i>n</i> (%)	Eyelid only, <i>n</i> (%)	Eyelid + face only, <i>n</i> (%)	Eyelid, face + other, <i>n</i> (%)	Eyelid + other; no face, <i>n</i> (%)	Patients patch tested for non-eyelid dermatitis, <i>n</i> (%)	All patch-tested patients, <i>n</i> (%)
Total patients	105	54	23	10	18	1110	1215
Total females	93 (88.6)	46 (85.2)	22 (95.7)	9 (90)	16 (88.9)	658 (59.3)	751 (61.8)
Total males	12 (11.4)	8 (14.8)	1 (4.3)	1 (10)	2 (11.1)	452 (40.7)	464 (38.2)
Total Caucasian	87 (82.8)	46 (85.2)	19 (82.6)	8 (80)	14 (77.8)	950 (85.6)	1037 (85.4)
Total black	11 (10.5)	4 (7.4)	3 (13.0)	2 (20)	2 (11.1)	97 (8.7)	108 (8.9)
Total Hispanic	2 (1.9)	0	0	0	2 (11.1)	27 (2.4)	29 (2.4)
Total Asian	5 (4.8)	4 (7.4)	1 (4.3)	0	0	17 (1.5)	22 (1.8)
Age (years)							
0–20	2 (1.9)	1	1	0	0	35 (3.2)	37 (3.1)
21–30	5 (4.8)	3	0	0	2	71 (6.4)	76 (6.3)
31–40	16 (15.2)	8	2	3	3	149 (13.4)	165 (13.6)
41–50	26 (24.8)	14	5	4	3	221 (19.9)	247 (20.3)
51–60	21 (20.0)	9	7	1	4	258 (23.2)	279 (23.0)
61–70	23 (21.9)	13	5	2	3	161 (14.5)	184 (15.2)
71–80	9 (8.6)	4	2	0	3	136 (12.3)	145 (12.0)
>80	3 (2.9)	2	1	0	0	78 (7.0)	81 (6.7)
H/o eczema	13 (12.4)	6 (11.1)	3 (13.0)	1 (10)	3 (16.7)	126 (11.4)	139 (11.4)

H/o, history of atopic eczema.

88.6%) were more prevalent than in the non-eyelid dermatitis population ($P < 0.0001$, OR = 0.19; 95% CI, 0.09–0.3). 13 of these patients (12.4%) reported a history of atopic dermatitis, which was not significantly higher than the incidence of atopic dermatitis in the non-eyelid dermatitis patient database (11.4%; $P = 0.5196$). Eyelid dermatitis occurred most often in Caucasians (82.8%); however, this racial predilection was not significantly different from the population patch tested ($P = 0.1148$). A comparison of ages in the study population showed the prevalence of eyelid dermatitis to be greatest in the middle- to old-aged population (41–70 years). There was no statistical significance between the ages of patients presenting with eyelid dermatitis compared to those with dermatitis elsewhere although there was a trend in that 24.8% of all patients with eyelid dermatitis were between the ages of 41 and 50 ($P = 0.0984$ versus population of patients without eyelid dermatitis, in which 19.9% were in this age range). Of the 105 patients with eyelid dermatitis, the majority (51.4%; $n = 54$) had dermatitis confined to the eyelids, while 51 (48.6%) had other areas of cutaneous involvement along with eyelid dermatitis. Table 1 shows the demographic data for patients with dermatitis in the following areas: eyelid only; eyelid and face; eyelid, face, and another site; and eyelid and another site but not facial site. Table 2 shows the clinical diagnosis(es) of the eyelid dermatitis that was derived after the completion of patch testing.

As shown in Table 2, of the 54 patients with allergic-appearing eyelid dermatitis that involved only the eyelids, the majority of patients were determined to have seborrheic dermatitis (46.3%). Nonetheless, patch testing was important in the evaluation of our patients with isolated eyelid dermatitis in that 3 of the patients with seborrheic dermatitis had a secondary ACD and, in total, 19 (35.2%) patients had ACD.

In contrast to isolated eyelid involvement, when the eyelid dermatitis was associated with other cutaneous findings, ACD was the most likely aetiology. Of the 23 patients with dermatitis confined to the eyelids and face, 11 (47.8%) patients were determined to have ACD and 1 of these 11 patients had ACD superimposed on another dermatoses. Seborrheic dermatitis was the second most likely cause of dermatitis affecting both the eyelids and the face. Of the 10 patients with dermatitis of the eyelids, face, and another site, 7 (70.0%) were given a diagnosis of ACD, while among the 18 patients with dermatitis of the eyelids and another site but not the face, 9 (50%) were given a diagnosis of ACD.

Patients with a suspected ACD of the eyelids were patch tested with a variety of allergens. As shown in Table 3, the allergens that produced a positive, relevant reaction most frequently consisted of fragrance mix and other fragrance substances, metals (such as nickel sulfate and cobalt chloride), oleamidopropyl dimethylamine, topical antibiotics (such as neomycin and other aminoglycosides), and preservatives (such as benzalkonium chloride, and quaternium-15). The number of patients who had a positive relevant reaction to these and other specific allergen is shown in Table 3.

Of the 1215 patients patch tested in this 10-year study, 646 were diagnosed with ACD (53.2%). Of the 646 with ACD, a total of 112 had a positive reaction to fragrance mix and other fragrance substances including balsam of Peru, isoeugenol, eugenol, vanillin, and jasmine absolute. 13 of these subjects had an eyelid dermatitis caused by fragrances. Patients with eyelid dermatitis were more likely to be allergic to fragrances (28.3%) than patch-tested patients without eyelid involvement (15.3%; $P = 0.0423$). In addition, a statistically significant association between

Table 2. Final diagnoses in patients presenting with suspected allergic eyelid dermatitis

	Eyelid only, ($n = 54$), n (%)	Eyelid + face only ($n = 23$), n (%)	Eyelid, face + other ($n = 10$), n (%)	Eyelid + other; not face ($n = 18$), n (%)	All patients with eyelid dermatitis ($n = 105$), n (%)	All patients with non-eyelid dermatitis ^a ($n = 1110$), n (%)	All patch-tested patients ($n = 1215$), n (%)
ACD	19 (35.2)	11 (47.8)	7 (70.0)	9 (50.0)	46 (43.8)	600 (54.1)	646 (53.2)
Atopic dermatitis	2 (3.7)	1 (4.2)	0	0	3 (2.9)	50 (4.5)	53 (4.4)
ICD ^b	7 (13.0)	0	0	1 (5.5)	8 (7.6)	144 (13.0)	152 (12.5)
Other dermatitis	4 (7.4)	1 (4.2)	0	2 (11.1)	7 (6.7)	168 (15.1)	175 (14.4)
Other dermatoses	2 (3.7)	3 (13.0)	0	0	5 (4.8)	117 (10.5)	122 (10.0)
Psoriasis	0	1 (4.2)	0	3 (16.7)	4 (3.8)	141 (12.7)	145 (11.9)
Seborrheic dermatitis	25 (46.3)	7 (30.4)	3 (30.0)	3 (16.7)	38 (36.2)	29 (2.6)	67 (5.5)

ACD, allergic contact dermatitis.

^aTotal values may be >100% because some patients were given more than 1 clinical diagnosis.

^bICD, irritant contact dermatitis.

Table 3. Relevant allergens in allergic eyelid dermatitis

Allergens ^a	Number of patients (<i>n</i> = 46), <i>n</i> (%)	Description
Fragrance mix and other fragrances	13 (28.3)	Fragranced cosmetics
Nickel sulfate	6 (13.0)	Metal
Neomycin and other aminoglycosides	5 (10.9)	Topical antibiotic
Oleamidopropyl dimethylamine	5 (10.9)	Surfactant
Benzalkonium chloride	4 (8.7)	Preservative
Thiuram mix	4 (8.7)	Rubber accelerator
Quaternium-15	4 (8.7)	Preservative
2-Bromo-2-nitropane-1,3-diol	3 (6.5)	Preservative
Cobalt chloride	3 (6.5)	Metal
Formaldehyde	3 (6.5)	Preservative
Sodium gold thiosulfate	3 (6.5)	Metal
Tosylamide formaldehyde resin	3 (6.5)	Resin in nail lacquer
Amidoamine	2 (4.3)	Surfactant (contaminant)
Budesonide and other corticosteroids	2 (4.3)	Corticosteroid
Colophony	2 (4.3)	Cosmetic tackifier, fragrance
Diazolidinyl urea	2 (4.3)	Preservative
Ethylenediamine dihydrochloride	2 (4.3)	Stabilizer and emulsifier
Imidazolidinyl urea	2 (4.3)	Preservative
Lanolin alcohol	2 (4.3)	Vehicle
Methyl hydroquinone	2 (4.3)	Antioxidant
Methylchloroisothiazolinone	2 (4.3)	Preservative
Methyldibromoglutaronitrile	2 (4.3)	Preservative
Thimerosal	2 (4.3)	Preservative
Ammonium persulfate	1 (2.2)	Hair bleach
Benzoyl peroxide	1 (2.2)	Medicament
Black rubber mix	1 (2.2)	Rubber accelerator
Cocamidopropyl betaine	1 (2.2)	Surfactant
Disperse blue 106	1 (2.2)	Dye
DMDM ^b hydantoin	1 (2.2)	Preservative
Ethyl acrylate	1 (2.2)	Nail adhesive
Glyceryl ricinoleate	1 (2.2)	Surfactant/emulsifier
Mixed dialkylthioureas	1 (2.2)	Rubber accelerator
Octyl dimethyl PABA ^c	1 (2.2)	Sunscreen agent
Polymyxin B sulfate	1 (2.2)	Topical antibiotic
Polysorbate 80	1 (2.2)	Surfactant/emulsifier
<i>p</i> -Phenylenediamine	1 (2.2)	Dye
Sodium benzoate	1 (2.2)	Preservative

^aOther: 1 patient each allergic to unknown ingredient in branded cosmetic products Aveda Shampoo, Brocato Cleanser, Clinique eye benefits, Estee Lauder Fruition (2 patients), Eucerin lotion, KMS Silker Shampoo, Lange Formula II Shampoo, Mary Kay TimeWise, Neutrogena Liquid Cleanser, Nucleic Gel, Sally Hansen Nail Products, Timolol ophthalmic solution, Thick Infusion Shampoo, VO5 Shampoo, and White Rain Shampoo.

^bDMDM, dimethylol dimethyl hydantoin.

^cPABA, para-aminobenzoic acid.

oleamidopropyl dimethylamine and eyelid dermatitis was observed: of the 12 patients with a positive reaction to this allergen, 5 manifested a relevant eyelid dermatitis ($P = 0.0009$). Statistically significant associations between eyelid dermatitis and specific allergens also occurred with benzalkonium chloride ($P = 0.0392$) and tosylamide formaldehyde resin (TFR; $P = 0.0032$). In contrast, our eyelid dermatitis patients were no more likely to be allergic to nickel sulfate ($P = 0.1899$), neomycin, and other aminoglycosides ($P = 0.2392$), or budesonide and other corticosteroids ($P = 0.2935$) than was our non-eyelid dermatitis population.

Discussion

Despite the challenges in determining the exact cause of eyelid dermatitis based solely on history

and observed symptoms, many of the characteristics of the patients studied can be used by practitioners to narrow the differential diagnoses and causative agents. In our study, 8.6% of patients patch tested presented with eyelid dermatitis. Previous studies have published similar prevalence rates of 7.2–13.0% (3, 7, 9). On the basis of our results, it can be concluded that the vast majority of cases occur in females (88.6% versus 11.4%, $P < 0.0001$). This is in accordance with previous data reporting 79–90% of all patients with eyelid dermatitis are female, leading to the speculation that the increased use of cosmetic products among women is a leading factor (1–7). Although the majority of patients are between the ages of 41 and 50 years (24.8%), we found no statistical difference between the age at presentation in patients with eyelid dermatitis and the population of patients without

eyelid dermatitis ($P = 0.0984$). We also found no difference in the racial distribution ($P = 0.1148$) or concomitant atopy ($P = 0.5196$).

Similar to previous studies (1–7, 9), we found ACD to be the most frequent cause of eyelid dermatitis (43.8% of all cases), which in our analysis was followed by seborrhoeic dermatitis as the second most common cause (36.2%). Similar results were reported by Cooper and Shaw, who evaluated 232 patients patch tested for eyelid dermatitis and determined that 28.9% had ACD and 20.7% seborrhoeic dermatitis (3). These authors noted that their lower incidence of ACD may have been due to the fact that they patch tested all patients with eyelid dermatitis and diagnosed ACD only if current relevance of an allergen was definitely established (3).

Others have reported that seborrhoeic dermatitis accounted for only 3–6% of eyelid dermatitis cases (1, 5, 7). In our study, the percentage of patients with eyelid dermatitis due to seborrhoeic dermatitis was much higher even though we tested only those who we suspected to have ACD. The reason for this difference is not clear. Indeed, in our 'eyelid-only' group, seborrhoeic dermatitis comprised 46.3% of cases and was the most common cause, suggesting that this entity should be very high on the differential when patients present with isolated eyelid involvement. However, it should be noted that we had several cases where patients presented with seborrhoeic dermatitis and were discovered to have an associated ACD, suggesting that patients with recalcitrant seborrhoeic dermatitis need patch testing.

ACD was the leading diagnosis when eyelid dermatitis occurred concurrently with facial dermatitis (47.8%), in a non-facial site (50.0%), or in the face and another body area (70.0%). Cooper and Shaw also found that the rate of ACD is increased in patients with both eyelid and facial dermatitis (35.4%) than in those with eyelid dermatitis alone (29.2%) (3).

Fragrance mix and other fragrances resulted in the greatest number of relevant reactions and, despite being among the more common allergens in the non-eyelid dermatitis group, demonstrated a statistically significant increase among patients with eyelid dermatitis ($P = 0.0423$). Other studies have also demonstrated fragrances to be leading allergens in eyelid dermatitis (1, 5–7). Nickel has repeatedly been a leading allergen in the eyelid group (13.0%), but we were unable to find a significant difference compared to patients without eyelid dermatitis ($P = 0.1899$).

Nickel sensitization (and often concomitantly cobalt) has been speculated to occur from direct contact with metallic objects (such as eyelash curlers and spectacle frames) and with eye makeup

(such as eye shadows and mascaras). Because most cosmetic products do not list nickel as an ingredient, its presence, as determined by previous studies after nickel spot testing, has been thought to result from contamination during manufacture (4). In addition, metals are also easily transferred by the hands after handling items such as keys, coins, and other such metallic objects and may cause only dermatitis in eyelid due to the thin, sensitive periorbital skin (2).

In addition to high rates of reactivity to fragrances and metals, we found that oleamidopropyl dimethylamine, a surfactant/emulsifier in numerous cosmetic products, was a leading cause of allergic eyelid dermatitis. 5 of the total 12 patients with positive reactions to oleamidopropyl dimethylamine manifested eyelid disease ($P = 0.0009$). De Groot determined that 11% of the 119 patients with proven cosmetic-related ACD were allergic to oleamidopropyl dimethylamine and concluded that its presence in a concentration of at least 0.3% in stay-on cosmetics, when applied to damaged or periorbital skin, carries a definite risk of eliciting reactions (10). These patients may also show cross-reactivity to other related amidoamine type emulsifiers and should probably avoid this entire class (10).

Benzalkonium chloride was another substance that proved to be a significant cause of allergic eyelid dermatitis ($P = 0.0392$). It is a quaternary ammonium cationic preservative widely used as an antiseptic. It is found in face washes, hand scrubs, aftershaves, cosmetics, detergents, deodorants, dentifrices, and other cosmetics and medicaments. Most importantly, it acts as an antimicrobial preservative in drugs, especially ophthalmic solutions, and should be an important allergen to consider when a history of eye drop use is elicited.

TFR, found in nail varnish, is a well-known allergen for inducing allergic eyelid dermatitis. Among all patients patch tested, it caused a positive reaction in a total of 5 patients, 3 of whom manifested eyelid dermatitis ($P = 0.0032$). Previous studies have published data demonstrating TFR to be a more common allergen in patients with eyelid dermatitis than in those without it (3, 4, 6). Artificial nail products, which contain acrylates, have been reported to be important contributors as well (4) although in our study, only 1 patient with eyelid dermatitis was allergic to ethyl acrylate. It has been found that nail products contribute to eyelid dermatitis about 10% of the time (4).

While the nature of the allergens found to be relevant to eyelid dermatitis may differ between the USA and other parts of the world due to the frequency and concentrations with which certain substances (such as preservatives, fragrances,

medicaments, etc) are used, our results show that the majority of the allergens inducing ACD of the eyelids in the USA are not present on the TRUE test, the only patch test material approved by the Food and Drug Administration (FDA) for use in the USA. Among these non-FDA approved allergens are oleamidopropyl dimethylamine, benzalkonium chloride, and TFR. In fact, the only allergens present on the TRUE test from the list in Table 3 are fragrances, nickel, cobalt, neomycin, thiuram mix, quaternium-15, formaldehyde, colophony, ethylenediamine dihydrochloride, lanolin alcohol, methylchloroisothiazolinone/methylisothiazolinone, thimerosal, and *p*-phenylenediamine. Because the bulk of allergens responsible for allergic eyelid dermatitis are not present on the TRUE test, it is important to test patients with eyelid dermatitis with more than just the TRUE test panels.

In conclusion, one must always be highly suspicious that ACD is a factor in eyelid dermatitis, whether as a primary process or one superimposed on a pre-existing condition. This is especially true when the dermatitis involves the eyelids and non-facial sites. Although eyelid dermatitis is challenging to diagnose and treat, with a thorough history and appropriate patch testing, an accurate diagnosis can be made and the patient properly managed.

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