

Periorbital dermatitis in 4779 patients – patch test results during a 10-year period

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Summary

Background. The thinness of the periorbital skin may facilitate allergen penetration, making this area particularly susceptible to sensitization.

Material and methods. For the cross-sectional study, data were collected by the 57 participating centres of the Information Network of Departments of Dermatology. A total of 101 403 patients patch tested between January 2001 and December 2010 were included. Of these, 4779 patients suffered from periorbital dermatitis.

Results. Two major subgroups with different general epidemiological data and sensitization to specific allergens have to be considered: (i) young females with increased rates of skin atopy and allergies, particularly from cosmetic and skin care products; and (ii) older subjects with allergy to topical medications. The prevalence of sensitization to ophthalmic allergens is generally less than that to environmental allergens.

Conclusions. Allergic contact dermatitis is a leading cause of periorbital dermatitis. Patch testing should be considered in all patients with periorbital dermatitis when contact allergy is suspected, in order to identify and avoid offending allergens.

Key words: allergy; antibiotics; patch testing; periorbital dermatitis; preservatives.

Allergic contact dermatitis is a common disease in the periorbital area (1–4); this may be related to the extremely thin nature of the periorbital skin, which facilitates the penetration of potential allergens. Sources of allergen transfer include the intentional application of topical medications or cosmetics to and/or around the eyes or via a partner, exposure to droplets or particles in the atmosphere leading to 'airborne contact dermatitis', and transfer of allergens from other body sites by the hands (ectopic dermatitis) (1).

Allergic periorbital dermatitis is an inflammatory process with clinical signs of erythema, itching, oedema,

and scaling of the periorbital region (5). Subsequent scratching of the periorbital skin may induce infection, disturbance in normal tearing dynamics, and loss of eyelashes. Early diagnosis and removal of the offending agent is therefore important to prevent recurrences.

To assess the current spectrum of allergens related to periorbital dermatitis, we conducted a retrospective cross-sectional analysis over the past 10 years, with the following objectives:

- (1) to identify the most common allergens in patients referred with suspected contact allergy of the periorbital area in a large cohort of patients,
- (2) to conduct subgroup analysis for those referred with periorbital dermatitis related to topical ophthalmic medication and subjects referred for other reasons, and
- (3) to compare periorbital patients with all other patients tested without involvement of the

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periorbital area (controls) in view of significant findings in the clinical data and patch test results.

Materials and Methods

The Information Network of Departments of Dermatology (www.ivdk.org), the contact allergy surveillance network in Germany, Switzerland, and Austria, has been described elsewhere (6, 7). Briefly, results obtained in the 101 403 patients patch tested in the participating 57 specialized centres between January 2001 and December 2010 were, at each location, electronically recorded, along with important demographic and clinical data according to a standardized questionnaire. All individuals underwent patch testing with a baseline series (29 allergens) and with supplemental series. Patch testing and reading of reactions was performed according to international recommendations (8), further refined by the German Contact Dermatitis Research Group (9). Commercial allergens were purchased from Almirall-Hermal (Reinbek, Germany). Patch tests were left on the back for 1 day (20% of participating centres) or 2 days (80% of participating centres), and test sites were evaluated at least at D2, D3, and, in some cases, at D4. In 20% of participating centres, there was also a reading at D1. In this analysis, only D3 and D4 readings were used. All data were transmitted to the data centre in Göttingen (Germany) in an anonymous format twice yearly, where they were checked and, if they satisfied internal quality criteria (10), analysed according to international guidelines (11).

For the comparative analysis, four groups were identified:

- (1) Periorbital group: patients referred with suspected contact allergy exclusively of the periorbital area, that is, no involvement of other body sites documented.
- (2) Periorbital medication subgroup: patients referred with suspected contact allergy to topical ophthalmic preparations.
- (3) Periorbital others subgroup: patients referred with suspected contact allergy to substances other than ophthalmic preparations and medications.
- (4) Controls: all other patients, excluding all subjects with (even only partial) involvement of the periorbital area.

Data management and statistical analysis were carried out with the statistical software package SASTM (Version 9.2; SAS Institute, Cary, NC, USA). Patients were characterized by use of the modified MOAHLFA index (Table 1). MOAHLFA is an acronym for male, occupational dermatitis, past or present atopic eczema, hand, leg and face dermatitis, and age ≥ 40 years (12). For data analysis, reactions were dichotomized as positive (+, ++, +++) and negative in terms of not allergic (negative, doubtful and irritant reactions). Frequencies of sensitization (as percentage of patients tested) were calculated as is, and as proportions standardized for sex and age, both accompanied by the 95% confidence interval. For most common allergens (Table 2), only standardized proportions are shown. Age and sex standardization of sensitization prevalence rates observed in the four subgroups allowed a comparison unconfounded by these two important factors. Patch test results were analysed regarding the total period, and stratified for sex.

Table 1. Proportion of males, subjects with an occupational background, subjects with atopic eczema, and age of patients within the four groups investigated

	Periorbital ALL 4779	Periorbital MEDS 1730	Periorbital OTHERS 3049	Controls 96 624	<i>p</i> -value Controls versus periorbital ALL	<i>p</i> -value Periorbital MEDS versus periorbital OTHERS
Males	905 18.9	435 25.1	470 15.4	37.196 38.5	< 0.0001	< 0.0001
Occupational dermatoses	172 3.6	17 1.0	155 5.1	15.078 15.6	< 0.0001	< 0.0001
Atopic eczema	1.249 26.1	379 21.9	870 28.5	17.209 17.8	< 0.0001	< 0.0001
Age ≥ 40 years	3.527 73.8	1.455 84.1	2.072 68.0	67.284 69.6	< 0.0001	< 0.0001

Periorbital group (ALL): all subjects tested for suspected contact allergy exclusively of the periorbital area. Periorbital medication subgroup (MEDS): suspected contact allergy to topical ophthalmic preparations. Periorbital others subgroup (OTHERS): suspected contact allergy to substances other than ophthalmic preparations and medications.

Table 2. Most common positive tested allergens among all periorbital dermatitis patients and subgroups (shown for allergens reaching at least 1% positive reactions among all periorbital dermatitis patients)

Allergens	n tested Periorbital ALL	Positive n % std	95% CI	n tested Periorbital MEDS	Positive n % std	95% CI	n tested Periorbital OTHERS	Positive n % std	95% CI	n tested Controls	Positive n % std CONTROLS	95% CI Controls
Nickel(II) sulfate.6H ₂ O	4340	796 17.5	16.3–18.7	1573	198 15.2	12.7–17.7	2767	598 18.9	17.4–20.4	87 162	12 670 16.8	16.5–17.1
Toluene 2,5-diamine	514	39 10.6	4.3–16.8	114	11 5.3	1.6–9.1	400	28 14.5	2.1–26.9	5994	944 16.2	15.1–17.3
Thimerosal	2490	179 9.3	7.8–10.9	1305	75 9.5	6.7–12.2	1185	104 9.8	7.8–11.8	22 527	1515 8.4	8.0–8.8
Phenylmercuric acetate	884	85 8.3	6.3–10.3	502	55 9.1	5.7–12.5	382	30 7.1	4.5–9.8	10 864	615 5.6	5.2–6.1
Balsam of Tolu	399	32 7.9	4.7–11.1	61	8 9.3	3.1–15.5	338	24 7.4	3.7–11.1	5296	555 9.1	8.3–9.9
Povidone iodine	531	42 6.7	4.5–8.9	206	17 6.8	2.7–10.9	325	25 7.3	4.2–10.5	18 105	1519 7.5	7.1–7.9
Fragrance mix I	4394	306 6.2	5.4–7.0	1587	116 6.2	4.7–7.7	2807	190 6.1	5.1–7.0	87 447	7040 7.3	7.1–7.4
Gentamicin sulfate	503	33 5.6	3.3–7.8	332	24 5.2	2.4–8.0	171	9 4.4	1.3–7.5	15 240	452 3.0	2.6–3.4
<i>Myroxylon perei</i>	4384	281 5.3	4.6–6.0	1584	121 5.9	4.5–7.3	2800	160 5.0	4.1–5.9	87 480	7243 7.1	6.9–7.2
Cobalt(II) chloride.6H ₂ O	4364	221 4.9	4.2–5.7	1577	65 4.8	3.3–6.3	2787	156 5.1	4.2–6.0	87 471	5189 6.6	6.4–6.8
Fragrance mix II	3007	148 4.5	3.6–5.3	1047	48 4.1	2.5–5.8	1960	100 4.6	3.5–5.6	55 770	2761 4.6	4.4–4.8
Oakmoss absolute	1300	57 4.5	2.9–6.0	364	18 5.2	1.3–9.2	936	39 4.4	2.6–6.2	19 830	983 4.2	3.9–4.5
Neomycin	3042	128 3.8	3.0–4.6	1421	80 4.6	3.2–6.0	1621	48 2.7	1.8–3.6	47 996	1097 1.9	1.8–2.0
Colophonium	4386	155 3.5	2.8–4.1	1586	52 3.4	2.1–4.7	2800	103 3.6	2.8–4.3	87 663	3848 4.3	4.1–4.4
Sodium metabisulfite	1996	76 3.5	2.3–4.6	1197	43 3.9	2.0–5.8	799	33 3.2	2.1–4.4	7876	259 2.9	2.6–3.3
Kanamycin sulfate	1819	69 3.5	2.3–4.7	1162	57 4.3	2.5–6.1	657	12 2.1	0.3–3.8	2053	40 1.4	0.9–1.8
Ammoniated mercury or mercury amidochloride	1841	48 3.0	2.0–3.9	708	10 1.6	0.4–2.8	1133	38 3.6	2.4–4.8	47 487	1482 3.6	3.4–3.8
Potassium dichromate	4379	123 2.9	2.3–3.5	1582	47 3.6	2.2–5.0	2797	76 2.6	1.9–3.3	87 612	4481 4.9	4.8–5.1

Table 2. Continued

Allergens	n tested Periorbital ALL	Positive n % std	95% CI	n tested Periorbital MEDS	Positive n % std	95% CI	n tested Periorbital OTHERS	Positive n % std	95% CI	n tested Controls	Positive n % std CONTROLS	95% CI Controls
Octyl gallate	3407	95 2.8	2.1–3.5	1200	40 2.6	1.5–3.7	2207	55 2.7	1.8–3.6	59 508	1439 2.2	2.1–2.3
<i>p</i> -Phenylenediamine base (CI 76060)	1799	62 2.8	2.0–3.6	680	22 1.9	1.1–2.7	1119	40 3.0	2.0–4.0	38 425	1715 4.6	4.4–4.8
Methyldibromo glutaronitrile/2-phenoxyethanol isoeugenol	1433 1395	39 2.4 3.4	1.6–3.3 1.4–3.1	552 405	12 2.1 5	0.4–3.7 0.1–1.4	881 990	27 3.1 2.8	1.8–4.4 1.6–3.9	32 665 21 476	1339 3.7 703	3.5–3.9 2.8–3.3
Methyldibromo glutaronitrile	3125	79 2.2	1.6–2.7	1101	30 2.4	1.3–3.4	2024	49 2.1	1.4–2.7	60 019	2321 3.4	3.2–3.5
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	4222	97 2.0	1.6–2.5	1527	27 1.3	0.7–1.8	2695	70 2.3	1.7–2.9	82 830	1914 2.3	2.2–2.4
Lanolin (wool alcohols)	4380	92 1.9	1.5–2.4	1584	42 2.5	1.5–3.4	2796	50 1.6	1.1–2.2	87 516	2655 2.8	2.7–2.9
Propolis cera	4385	91 1.9	1.4–2.4	1588	33 1.6	0.9–2.3	2797	58 2.2	1.5–2.8	87 537	2131 2.2	2.1–2.3
Epoxy resin	4385	57 1.7	1.2–2.3	1584	20 1.1	0.4–1.8	2801	37 2.0	1.2–2.7	86 686	1338 1.5	1.4–1.5
Phenylephrine-HCl	1822	41 1.7	1.0–2.4	1163	34 2.1	1.0–3.1	659	7 1.2	0.3–2.1	1919	23 0.8	0.4–1.2
Cocamidopropyl betaine	3576	55 1.6	1.1–2.0	1183	16 1.2	0.2–2.1	2359	40 1.6	1.0–2.1	61 555	1326 2.0	1.9–2.2
Methylchloroisothiazolinone/ methylisothiazolinone 3:1 in water	4388	80 1.5	1.1–1.9	1584	27 1.2	0.7–1.7	2804	53 1.6	1.1–2.0	87 762	2092 2.3	2.2–2.4
Benzalkonium chloride	2282	34 1.4	0.8–2.0	1255	22 1.5	0.6–2.4	1027	12 1.3	0.4–2.1	25 422	355 1.4	1.2–1.5
Turpentine peroxides	4381	58 1.3	0.9–1.7	1585	20 1.4	0.6–2.3	2796	38 1.3	0.8–1.8	87 457	1844 1.9	1.8–2.0
Formaldehyde	4383	50 1.2	0.8–1.5	1583	15 1.3	0.5–2.0	2800	35 1.1	0.7–1.6	87 592	1215 1.4	1.3–1.5
tert-Butylhydroquinone	3449	52 1.2	0.8–1.5	1583	15 1.3	0.4–2.1	2237	26 0.9	0.5–1.3	60 375	1381 2.0	1.8–2.1
Thiuram mix	4389	51 1.1	0.8–1.5	1586	20 0.9	0.4–1.4	2803	31 1.1	0.7–1.5	87 609	2077 2.3	2.2–2.4
Propylene glycol	3447	35 1.1	0.7–1.6	1212	10 0.7	0.2–1.2	2235	25 1.3	0.7–2.0	60 624	1127 1.8	1.7–1.9

CI, confidence interval; Std, standardized for sex and age.

Periorbital group (ALL): all subjects tested for suspected contact allergy exclusively of the periorbital area. Periorbital medication subgroup (MEDS): suspected contact allergy to topical ophthalmic preparations. Periorbital others subgroup (OTHERS): suspected contact allergy to substances other than ophthalmic preparations and medications.

Results

Patients patch tested for periorbital dermatitis (4779) constituted 4.7% of 101 403 investigated individuals in this 10-year period of observation. In our general clinical or demographic data, there were significantly more females referred for suspected contact allergy of the periorbital area and they more often had an atopic background, as shown in Table 1. Occupation-related visits were unusual in the subjects with periorbital dermatitis. Patients referred for evaluation of periorbital dermatitis other than that related to ophthalmic medications were, on average, statistically significantly younger than controls. In contrast, patients with periorbital dermatitis related to topical ophthalmic medications were significantly older than controls and the other periorbital subgroup. Patch test results of all periorbital patients tested showed the most common allergens to be the same as in the general population, such as metals, fragrances, and preservatives. For details of all four groups, see Table 2. In the subgroup tested for possible contact allergy to ophthalmic medications, increased rates of sensitization to the preservative phenylmercuric acetate, antibiotics (gentamicin, neomycin, and kanamycin) and the α -receptor antagonist phenylephrine-HCl were observed.

The leading final diagnoses after patch testing in all groups were allergic contact dermatitis and atopic eczema (Table 3). The highest rates of allergic contact dermatitis were found among the referrals with suspected contact allergy to topical ophthalmic medications (34.7%). This finding was significant when compared with 'other periorbital dermatitis' patients (30.4%) and controls (22.9%). Moreover, the final diagnosis of atopic eczema was significantly associated with 'periorbital dermatitis' as compared with controls (16.6% versus 7.7%). This was particularly true for the subgroup of 'other periorbital dermatitis' (18.4%). The number of patients diagnosed with irritant contact dermatitis did not differ remarkably between 'periorbital' patients and controls.

Discussion

Almost 5% of the total patch test population were exclusively tested for suspected contact allergy in the periorbital area in this 10-year period. The reported prevalence of patients with periorbital/eyelid dermatitis from other patch test clinics in the literature shows a wide variation, ranging between 3% and 21% (2, 5, 13–15). This finding can be attributed to different levels of sensitization in the

Table 3. Most common final diagnoses after patch testing

Final diagnoses	Periorbital ALL 4779	Periorbital MEDS 1730	Periorbital OTHERS 3049	Controls 96 624	<i>p</i> -value Controls versus periorbital ALL	<i>p</i> -value Periorbital MEDS versus periorbital OTHERS
Allergic contact dermatitis	1529	601	928	22 119	< 0.0001	0.002
Positive patch test result along with recent exposure to that allergen with skin worsening	32	34.7	30.4	22.9		
Atopic eczema	793	231	562	7477	< 0.0001	< 0.0001
Negative patch test result, personal or family history of flexural eczema	16.6	13.4	18.4	7.7		
Eczema (not classified)	659	234	425	6426	< 0.0001	n.s.
	13.8	13.5	13.9	6.7		
Exclude contact allergy	591	227	364	12 496	n.s.	n.s.
	12.4	13.1	11.9	12.9		
Irritant contact dermatitis	334	139	195	6696	n.s.	0.03
Dermatitis at the site of contact with the presence of a substance known to be an irritant	7.0	8	6.4	6.9		
Acute irritant contact dermatitis	140	50	90	1174	< 0.0001	n.s.
	2.9	2.9	3.0	1.2		
Airborne contact allergy	126	26	100	466	< 0.0001	0.0002
Exposure to droplets or particles in the atmosphere resulting in periorbital contact dermatitis	2.6	1.5	3.3	0.5		

n.s., not significant; final diagnoses of < 2% in the periorbital dermatitis group are not shown.

Periorbital group (ALL): all subjects tested for suspected contact allergy exclusively of the periorbital area. Periorbital medication subgroup (MEDS): suspected contact allergy to topical ophthalmic preparations. Periorbital others subgroup (OTHERS): suspected contact allergy to substances other than ophthalmic preparations and medications.

different countries, to the specialization of certain centres, meaning that they see a more or less selected group of patients at the end of a referral process, or to different study approaches, such as the inclusion of patients with only partial involvement of the periorbital area.

A predominance of females among subjects with periorbital dermatitis is well known from the literature, and has been attributed to the more common application of cosmetics and topical products to the face, particularly to the periorbital area (2, 4, 5). The proportion of females of 81.1% found in our study is similar to observations reported from the United States (88.6%) and southern Europe (90%) (5, 13).

Frequent sensitizers included metals, fragrances, and preservatives. The stable prevalence of commonly seen allergens probably reflects their extensive distribution in industry and everyday life. Nickel sulfate was the leading allergen in this and other studies patch testing patients with periorbital dermatitis (1, 2, 5). Sensitization to nickel is mostly acquired by prolonged and intense contact with nickel ions, for example when wearing jewellery (16, 17). As female sex was overrepresented among our periorbital dermatitis patients as compared with controls, sensitization to nickel may be a coincidence, and does not necessarily reflect ophthalmological problems. For a selected group of cases, allergic periorbital dermatitis may be caused by the application of nickel-containing eye cosmetics [eye shadows (18), mascara (19), eye pencils (20)] or by contact with metal-containing eyeglass frames or eyelash curlers. In addition, accidental transfer by hands contaminated with nickel ions still present from previous contact with metal coins, jewellery and other metal products may cause ectopic allergic contact dermatitis around the eyes (1, 3).

The sensitization rates of 6.2% for fragrance mix and 5.3% for *Myroxylon pereirae* are comparable to those in other studies describing 8–20% positive reactions to fragrance mix and 3.3–8% positive reactions to *M. pereirae* (2, 5, 14). As with nickel, transfer of fragrances from the hands to the face might be a relevant source of sensitization, as the face and the hands are the most commonly affected body sites regarding fragrance allergy (1, 21).

The top-ranking allergens among ophthalmic preparations were preservatives, with phenylmercuric acetate as the leading allergen, and antibiotics. The high rate of positive reactions to phenylmercuric acetate may be related to the fact that the initial patch test formula itself containing 0.05% in petrolatum may cause skin irritation that may be misinterpreted as a weak positive reaction. Hence, the true proportion of patients sensitized to phenylmercuric acetate is probably lower (2, 22, 23). After reduction of the test concentration to 0.01% pet. in 2003, the

proportion of positive reactions declined significantly, as did the number of doubtful and irritant reactions (detailed data not shown). An increased frequency of sensitization to antibiotics among patients with periorbital and eyelid dermatitis has been described previously in the literature (2, 4, 5, 24), and can be attributed to their widespread use for infection in and around the eyes.

Another high-ranking sensitizer was thimerosal. It was found as an additive in multi-dose eyedrops or eardrops in concentrations ranging from 0.001% to 0.004% (25, 26), contact lens solutions, mascara, and other cosmetics. However, the clinical relevance was stated to be low (27). It has been suggested that prior exposure related to vaccination in childhood, and not the use of ophthalmic products, resulted in the sensitization. Because of possible side-effects caused by ethyl mercury as a metabolic product of thimerosal, and eco-toxic considerations with regard to reducing mercury pollution of the environment, the US Centers of Disease Control and Prevention and the European Agency for the Evaluation of Medicinal Products issued a precautionary recommendation to eliminate thimerosal from vaccines in 1999 (28, 29). As many patients included in our data analysis were probably vaccinated before 1999 with thiomersal-containing vaccines, the proportion of sensitization to this allergen does not necessarily reflect ophthalmological problems. Moreover, the increasing use of preservative-free single-dose eyedrops will also probably reduce the rate of sensitization to this allergen. Consequently, thimerosal is likely of only historical relevance.

In accordance with the literature, allergic contact dermatitis was the top-ranking final diagnosis among patients presenting with periorbital diagnosis, although our rate of 32% is somewhat lower than described by others (43.8–72%) (5, 13, 14, 30).

If allergy testing is considered for suspected contact allergy in the periorbital region, certain specifics have to be considered. Regarding allergens, one should include substances that might come into contact with the hands, to account for incidental transfer by the hands. In patients with suspected contact allergy to ophthalmic products, tests with diluted pure substances from standardized ophthalmic series are recommended, but it is preferable to test the actual drops or cream. The repeated open application test may be used as a preliminary simple test. The conjunctival challenge test may also be helpful to prove allergy to topical ophthalmic products, if conjunctival symptoms have been reported.

If patch testing at the upper back fails to confirm allergic contact sensitization to suspicious allergens, tape stripping (31), enlarged test areas or higher patch test concentrations may increase test sensitivity. However,

because of heightened irritancy of the skin, false-positive results are also more likely.

Limitations

First, our study sample was drawn from patients who were referred to a dermatologist for patch testing; therefore, this study sample may not be representative of the general population. Second, patch testing is conventionally conducted on the upper back, and it is possible that the penetration of allergens and the susceptibility of truncal skin differ from those for periorbital skin, such that some of the weaker allergens inducing reactions in the periorbital area might not show up in the upper back. Third, in this analysis, only D3 and D4 readings were used. Thus, we might have overlooked some later-reacting allergens, in particular neomycin and gentamicin, which are known to often elicit patch test reactions beyond D3 (32).

Conclusions

In summary, our study is the largest investigation on this topic, including 4779 patients presenting with periorbital dermatitis over a 10-year period. The large sample size and standardized information regarding historical data, medical history and test results in the participating centres allowed us to obtain more insights into this diagnostic entity. Allergic contact dermatitis is a leading aetiological cause of dermatitis of the periorbital area, and patch testing should therefore be considered as a regular diagnostic tool. Two major subgroups with different general epidemiological data and sensitization to specific allergens have to be considered: (I) young females with increased rates of skin atopy and allergy, particularly from cosmetic and skin care products; and (II) older subjects with allergy to topical medications.

Important allergens to test in patient group I are included in commercially available standard, cosmetic and supplemental series. The prevalence of sensitization to ophthalmic allergens is generally less than that to environmental allergens, most likely because of the more extensive distribution of environmental allergens and the increased use of preservative-free (e.g. single-dose vials) ophthalmic preparations. If contact sensitization to ophthalmic preparations is suspected, testing with drops brought in by the patient should be considered, if feasible,

followed by break-down testing of identifiable ingredients to detect other emerging allergen sources, as many chemicals that are present in ophthalmic preparations are not available as commercial test allergens.

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