CONTACT ALLERGIC REACTIONS ON THE EYES AND EYELIDS

*GOOSSENS A.**

SUMMARY

Purpose: To determine the most important causes of contact allergic reactions on the eyes and eyelids.
Patients and Methods: This retrospective study provides an analysis of patch-test results obtained in a population of 1554 patients suffering from conjunctivitis and/or dermatitis on the eyelids, out of a total population of 9035 patients investigated for contact allergy between January 1990 and October 2003. If indicated, also prick testing with a latex extract was performed.
Results: 864 (56 %) of the patients with eye- and/or eyelid-involvement presented with a positive reaction to at least one of the contact allergens tested. The main sensitisation sources were topical pharmaceutical products (antibiotics, corticosteroids), cosmetics (fragrance components, preservatives, emulsifiers, hair-care and nail products), metals (nickel), rubber derivatives, resins (e.g. epoxy resin), and plants. Also latex-allergy (immediate-type sensitivity presenting as a contact-urticaria syndrome) was a frequent finding in such patients.
Conclusion: Contact allergy is a common cause of eyelid dermatitis in particular and the allergens may reach the skin in many different ways.

RÉSUMÉ

Buts: L'identification des sources de réactions d'allergie de contact les plus importantes au niveau des yeux et des paupières.
Patients et Méthodes: Cette étude rétrospective apporte une analyse des résultats de tests épicutanés obtenus chez 1554 patients souffrant d'une conjonctivite et/ou d'une dermatite aux paupières, parmi une population totale de 9035 patients ayant reçu des investigations allergologiques durant la période janvier 1990 à octobre 2003. Dans certains cas, des tests "prick" avec un extrait de latex ont également été effectués.
Résultats: 864 (56 %) des patients ayant des problèmes de conjonctivite et de dermatite localisées aux paupières, ont montré une réaction positive à au moins un des allergènes de contact testés. Les sources de sensibilisations les plus importantes se sont révélées être des produits pharmaceutiques à usage local (antibiotiques, corticostéroïdes), des produits cosmétiques (composants de parfum, conservateurs, émulsifiants, ingrédients de produits capillaires et de produits pour ongles), des métaux (nickel), des dérivés de caoutchouc, des résines (p.e. la résine époxy) et des plantes. L'allergie de type immédiat (se présentant comme un syndrome d'urticaire de contact) au latex a également été observée.
Conclusion: Des réactions d'allergie de contact sont souvent à base d'une dermatite de contact essentiellement localisée aux paupières et les allergènes peuvent atteindre la peau de différentes manières.

KEY WORDS

Allergy, contact dermatitis, allergens, eyes, eyelids.

MOTS-CLÉS

Allergie, dermatite de contact, allergènes, yeux, paupières.

.....

* *Department of Dermatology. University Hospital K.U.Leuven.*

received: 05.11.03
accepted: 20.12.03

INTRODUCTION

Allergic contact dermatitis has been considered the most common of the many dermatological conditions found with eyelid dermatitis. The differential diagnoses include irritant contact dermatitis, atopic eczema, seborrheic dermatitis, psoriasis, dermatomyositis, rosacea, cutaneous T-cell lymphoma, infections, and (contact)urticaria (4). The eyes (the mucosa itself being only rarely involved except for type I latex allergy), and particularly the eyelids are commonly affected by allergic contact dermatitis because the skin is very thin in this area. Hence, contact allergens do penetrate easily. Sometimes, even when an allergen comes in contact with another body site, they may constitute the only area affected, such as in the case of a hair-dye dermatitis which may express itself as a severe oedema of the eyelids only. The causal contact allergens may be of occupational or non-occupational origin and may reach the skin in various ways (6):

- by intentional application of the allergen, such as in the case of eye cosmetics;
- by direct contact with an allergen or allergen-contaminated surface, e.g. due to a pillow;
- by exposures to gases, droplets or particles in the atmosphere, which results in ''airborne'' dermatitis, an example being an occupationally-related epoxy-resin or wood dermatitis;
- by contact with spouses, partners, friends or colleagues who convey the allergens, to cause ''connubial'' or ''consort'' dermatitis, e.g. a hair-dye inducing a dermatitis in a wife's husband;
- by transfer from other sites on the body, generally the fingers, to more sensitive areas such as the face and the eyelids in particular. This is referred to as ''ectopic'' dermatitis, a typical example being nail varnish allergy;
- by systemic exposure in patients previously sensitized via the skin. This is the case, for example, in a patient previously sensitized to a topical drug (e.g. neomycin) who presents with symmetric lesions on the body, often including the eyelids, after systemic exposure (ingestion, injection,...) to the same or a chemically-related drug (e.g. gentamycin);
- in combination with exposure to the sun, as in the case with photoallergens such as certain sunscreen agents; however, the eyelids are only exceptionally involved since, with photoallergic contact dermatitis, the anatomically-shadowed portions of the body are most often spared;
- as an expression of a spread or a generalization of a contact dermatitis elsewhere on the body, e.g. in a leg-ulcer patient suffering from an allergy to a locally applied pharmaceutical product.

The following concerns the results of a retrospective study of patients with conjunctivitis and/or eyelid dermatitis who were referred for patch testing to our Contact Allergy Unit.

PATIENTS AND METHODS

A total population of 9035 patients (3120 men, 5915 women), of whom 1545 (17 %), (321 men, 1224 women) suffered from conjunctivitis and/or eyelid dermatitis as a primary or secondary complaint, were investigated for contact allergy between January 1990 and October 2003. They were all patch tested with a European standard series (obtained from Hermal, Hamburg, Germany), with Belgian additions [propylene glycol, tosyl/formaldehyde resin (present in nail varnish)], a mixture of the preservative agents methyldibromoglutaronitrile and phenoxyethanol, Amerchol L101 (lanolin alcohol and mineral oil) and sorbitan sesquioleate (an emulsifier). Moreover, most of them were also tested with other series (e.g. cosmetics series), with the products brought in by the patients, along with the ingredients present in them. The patch-test materials applied were van der Bend chambers (van der Bend, Brielle, the Netherlands) secured with Micropore tape (Healthcare 3M, Borken, Germany) and Mefix Mölnlycke, Göteborg, Sweden). The reading of the patch-test results was performed, according to standard criteria, after 2 and 4, (occasionally) 3 days, and sometimes also later. When immediate-type allergic reactions were suspected, such as, for example, in the contact-urticaria syndrome with latex allergy, also prick testing with a latex ex-

tract (Stallergènes, Waterloo, Belgium) was performed, using histamine and saline as a control.

RESULTS

864 (56 %) out of the 1545 patients with eye- or eyelid involvement, i.e. 136 men and 728 women (respectively 42,4 % and 59,5 %) presented with at least one positive patch test reaction. The most important routinely and non-routinely tested allergens identified are given in Table 1 and 2, respectively. However, the order of importance observed is not necessarily relevant for the symptoms on the eyes or eyelids. For example, to have an idea about the allergens typical for this area, we did compare the results of positive patch tests obtained with a group of 280 patients suffering from lesions located only on the eyes/eyelids, with the results obtained in a group of 4186 patients not having lesions on this body site. The contact allergens specifically relevant for eyelid dermatitis (chi-square analysis) were found to be: nickel, neomycin, methyl-(chloro)isothiazolinone, thiomersal, tixocortol pivalate {being a marker for sensitivity to corticosteroids of the hydrocortisone-, and (methyl)-prednisolone-type} (5), gentamycin, tobramycin (and related cross-reacting aminoglycosides), and cocamidopropyl betaine. In this study, 2 allergens were found not to be specifically related to eyelid dermatitis in particular, i.e. p-phenylenediamine (PPD) and potassium dichromate. PPD is a component of oxidative-type hair-dyes that may cause eyelid dermatitis (!) but which is also a marker for sensitivity to other para-aminobenzene compounds such as benzocaine, textile dyes (which, by transfer by the hands such as in the case of disperse blue 106, may also be responsible for eyelid dermatitis) and rubber and plastic additives; potassium dichromate is an allergen oc-

Table 1: *Number of positive reactions to the most frequently observed routinely tested contact allergens in patients with eyelid dermatitis.*

Order	Allergen	N Women	N Men	N Total
1	Nickel sulfate	324	3	327
2	Fragrance-mix	111	19	130
3	p-phenylenediamine	62	15	77
	Cobalt chloride	75	2	77
4	Myroxeilon Pereirae or B. of Peru	58	15	73
5	Colophonium	58	5	63
6	Lanolin Alcohols	45	12	57
7	Amerchol L101	39	7	46
8	Neomycin	32	12	44
9	Thiuram-mix	26	9	35
10	Methyl(chloro)isothiazolinone	26	3	29
	Potassium dichromate	23	6	29
11	MDBGN*-Phenoxyethanol	22	6	28
	Tixocortol pivalate **	25	3	28
12	Budesonide**	23	4	27
13	Epoxy resin	14	11	25
14	Benzocaine	15	5	20
15	Sesquiterpene lactone-mix	11	7	18
16	Formaldehyde	16	1	17
	Tosylamide/Formaldehyde resin	17	0	17
17	Sorbitan Sesquioleate	8	3	11
18	Propylene glycol	9	1	10

* MDBGN= Methyldibromoglutaronitrile

** Markers for sensitivity to other corticosteroïds: tixocortol pivalate for hydrocortisone-and (methyl)prednisolone type; budesonide for other acetonides (e.g. triamcinolone acetonide) and certain esters (e.g. hydrocortisone-17 butyrate and methylprednisolone aceponate) (5)

Table 2: *Number of positive reactions to the most frequently observed non-routinely tested contact allergens in patients with eyelid dermatitis.*

Order	Allergen	N Women	N Men	N Total
1	Thimerosal	39	7	46
2	Oak moss	28	2	30
3	Diaminodiphenylmethane	21	8	29
4	MDBGN	23	3	26
5	Isoeugenol	19	4	23
6	Hydrocortisone	18	2	20
7	Gentamycin/ Tobramycin	13/12	5/6	18
8	Hydrocort-17-butyrate	16	1	17
	Cocamidopropyl betaine	15	2	17
	Sodium metabisulfite	15	2	17
9	Ethylenediamine HCL	15	1	16
10	Mercury	12	2	14
11	Lyral	13	0	13
	Limonene oxidized	12	1	13
	Phenylmercuriborate	11	2	13
12	Chloroacetamide	10	2	12
	Diazolidinyl urea	11	1	12
	Hydroxycitronellal	11	1	12
13	Eugenol	7	4	11
14	Imidazolidinyl urea	9	1	10
15	Cetyl alcohol	8	1	9
	Carba-mix	6	3	9
	Polymyxine B sulfate	7	2	9
	Cinnamyl alcohol	7	2	9
16	Chloramphenicol	4	4	8
17	Bromonitropropanediol	7	0	7
	Disperse blue 106	7	0	7
	Cinnamal	6	1	7
18	Palladium chloride	6	0	6
	Toluene diamine	5	1	6
	Phenylephrine	5	1	6
	Benzoyl peroxide	4	2	6
	Cocamidopropyl PG-dimon.	6	0	6
19	Glutaraldehyde	4	1	5
	Benzofenone-3	5	0	5
	Atropine	4	1	5
	Nonoxynol-9	5	0	5
	Benzalkonium chloride	3	2	5
	Ammonium persulfate	5	0	5
20	Glyceryl thioglycolate.	4	0	4
	Minoxidil	3	1	4
	Propacetamol HCL	3	1	4

curring in cement and chromium-tanned leather (shoe-dermatitis!), but occasionally also in eye-make- up.

Furthermore, there were also other contact allergens that gave less frequently positive reactions but were considered relevant for the complaints: 3 reactions were observed to primine (primula), gold sodiumthiosulphate, hydroxyethyl-methacrylate or HEMA (an allergen present in nail cosmetics and dental products), rani-

tidine, cephalosporines and semi-synthetic penicillins (drugs administered by health care personnel, [2]), lauramine oxide (an emulsifier present in a surgical scrub) and homatropine; metipranolol and timolol were observed twice, and betaxolol, dipivefrine, oxytetracycline, rifamycin, and tropicamide once as allergens, the latter substances having been applied via ophthalmic preparations only. Examples of drug-induced reactions with eczema on the eyelids were colchicine and mitomycine C. The list of allergens mentioned is, of course, not exhaustive. Positive prick tests to latex were found in 34 patients (30 women and 4 men).

DISCUSSION

Contact allergic reactions were observed in 56 % of the patients suffering from conjunctivitis and/or eyelid dermatitis as a primary or secondary complaint. This is in agreement with literature data (1, 4), according to which allergic contact dermatitis is indeed a common cause of eyelid dermatitis and occurs between 46 and 74 % in such patients. Also the nature of the most important sensitisation sources was very similar to those mentioned by these authors.

Pharmaceutical Products

In our study, the most important allergens were topical pharmaceutical products, i.e. active principles, vehicle components and preservative agents present in ophthalmic preparations. Among the active principles: antibiotics such as neomycin and related aminoglycosides in particular, chloramphenicol, polymyxin B, oxytetracycline and rifamycin; antiseptics (mostly mercurials); corticosteroids, mydriatic agents (phenylephrine, atropine, homatropine, tropicamide) and beta-blocking agents (betaxolol, metapronolol, timolol); as vehicle components, lanolin alcohols, cetyl alcohol, sorbitan sesquioleate and propylene glycol; as preservative agents thiomersal and benzalkonium chloride, and as antioxidants, sodium metabisulfite and ethylenediamine HCl. Of course, some of these ingredients were also present in pharmaceutical products applied elsewhere on the body and did cause reactions on the eyelids by transfer by the hands, by contamination (e.g. via a pillow), or as an expression of a generalization of a contact dermatitis elsewhere on the body. Examples are benzoyl peroxide (used to treat acne) and minoxidil (used to stimulate hair growth on the scalp), and nonoxynol, an emulsifier present in several local antiseptics used in wound treatment. A few cases of eyelid dermatitis were also found to be due to systemic medication handled by health care personnel (2), i.e. propacetamol (to relieve pain), ranitidine (to treat peptic ulcer), and antibiotics of the cephalosporin and penicillin type. Also disinfectants such as glutaraldehyde that typically induces airborne dermatitis, and lauramine oxide, an emulsifier present in a surgical scrub, were responsible for eyelid dermatitis.

Cosmetics

Fragrance components, preservative agents, emulsifiers, hair-care products and nail-cosmetic ingredients were identified as allergenic culprits. To detect perfume allergy, markers in the standard series are the following: fragrance-mix (a mixture of 8 fragrance chemicals that were often found to be positive, i.e. oak moss, isoeugenol, eugenol, cinnamyl alcohol, cinnamal, hydroxycitronellal), balsam of Peru (a natural mixture of several ingredients used in perfumery), and colophonium (a resin obtained from pine trees that may also cause airborne dermatitis in violin players and in sportsmen who use it as a powder to have a better handgrip). Moreover, also oxidized limonene and Lyral® have become important fragrance allergens in recent years (3). Fragrance components most often induce eyelid dermatitis by airborne exposure to sprays containing them, and sometimes also via products used by someone else (''connubial'' or ''consort'' dermatitis).

The most important preservative allergens found in this area were the methyl- and methylchloroisothiazolinone- and methyldibromoglutaronitrile (MDBGN)-phenoxyethanol mixtures, followed by formaldehyde and its releasers, i.e. imidazolidinyl-and diazolidinyl urea, and bromonitropropanediol. Altough chloroacetamide is a potent allergen that may cause cosmetic dermatitis, its presence in house paints has also caused airborne eyelid dermatitis.

With regard to emulsifiers, cocamidopropyl betaine (an emulsifier used in cleansing products including eye-make-up removers, contact lens

solutions and shampoos), and its derivative cocamidopropyl PG-dimonium chloride (an emulsifier present in a facial product for "sensitive" skin that produced several reactions a few years ago) were the most frequent causes.
Hair-care products do often cause problems around the scalp, i.e. ears, neck, and forehead, and particularly on the eyelids. This is the case for p-phenylene-diamine (PPD) and toluene diamine (hairdyes), glyceryl thioglycolate (permanent wave solutions), and ammonium persulfate (which may also cause contact urticaria due to direct contact in clients, but also in hairdressers by airborne contact with this hair-bleaching powder). Moreover, tosylamide/formaldehyde resin, the most important allergen in nail varnish, as well as (meth)acrylate derivatives (cfr. infra), i.e. hydroxyethyl-methacrylate (HEMA) in particular, present in artificial and gel nails, were causes of airborne dermatitis on the face and the eyelids. Finally, exceptionally sunscreens such as benzophenone-3 were the cause of (photo)allergic contact dermatitis on this location, and metals may be involved too (cfr. infra).

Metals

Nickel (and concomitantly often also cobalt) have been implicated in eyelid dermatitis as allergens by direct contact with metallic objects such as an eyelash curler and spectacle frames, and also in mascara and eye-makeup. However, these metals are also easily transferred by the hands handling keys, coins, and other metallic objects. Cobalt (vitamin B12) was also identified as an airborne allergen in animal feed. Palladium chloride may cross react with nickel, while gold allergy has been found to be related to eyelid dermatitis, the reason of which is unclear (4).

Rubber derivatives and resins

Rubber materials may induce allergic contact dermatitis, which is due to rubber additives such as thiuram-derivatives and carbamates, often present in gloves causing both eczema on the hands and the eyelids. Of course, rubber additives have also caused contact allergic reactions by direct contact with, for example, an eyelash curler or swimming goggles. Water-soluble proteins in natural rubber (latex) are responsible for the contact urticaria syndrome, i.e. cutaneous symptoms often associated with conjunctivitis, rhinitis, and respiratory symptoms.
As to the resins, epoxy resin dermatitis is typically expressed on the eyelids due to airborne contact. This can be due to contact allergy to the resin itself, to certain diluents but also to hardeners such as, for example, diaminodiphenylmethane. The latter is a para-aminobenzene compound mostly cross-reacting with p-phenylenediamine and related materials, but it sometimes also indicates contact allergy to isocyanates in polyurethane resins. Some other resins were already mentioned before, including (meth)acrylate derivatives that were also causes of airborne eyelid dermatitis (or transfer by hands) in dentists and dental technicians. In contrast to the uncured monomers present in dental resins, the polymers (e.g. as in contact lenses) are not responsible for contact allergic reactions.

Plants

Woods and plants most often cause dermatitis via transfer by the hands, or by airborne contact. In our series, sesquiterpene lactones, allergens being present mainly in *Asteraceae or Compositae* such as chrysanthemum, camomile, sunflowers, etc. were the most frequent causes of eyelid dermatitis. The allergens in primula were particularly responsible for dermatitis by transfer with the fingers.

CONCLUSION

Allergic contact dermatitis is a common cause of eyelid dermatitis. The causal contact allergens may be of occupational or non-occupational origin and may reach the skin in various ways. The main sensitization sources were topical pharmaceutical products, cosmetics, metals, rubber derivatives, resins, and plants. Latex-allergy was responsible for immediate-type sensitivity presenting as a contact-urticaria syndrome including conjunctivitis.

REFERENCES

(1) AYALA F., FABBROCINI G., BACHILEGA R., BERARDESCO E., CARAFFINI S., CORAZZA M., FLORI M. L., FRANCALANCI S., GUARRERA M., LISI P., SANTUCCI B., SCHENA D., SUPPA F., VALSECCHI R., VINCENZI C., and BALATO N. – Eyelid dermatitis: an evaluation of 447 patients. Am. J. Cont. Derm. 2003, 14, 69-74.

(2) GIELEN K., GOOSSENS A. – Occupational allergic contact dermatitis from drugs in healthcare workers. Contact Dermatitis 2001, 45, 273-279.

(3) GOOSSENS A., LEPOITTEVIN J.-P. – Allergie de contact aux cosmétiques et aux composants de parfums: aspects cliniques, chimiques et diagnostiques nouveaux. Revue Française d'Allergologie et d'Immunologie Clinique 2003, 43, 294-300.

(4) GUIN J.D. – Eyelid dermatitis: Experience in 203 cases. J. Am. Acad. Dermatol. 2002, 47, 755-765.

(5) MATURA M., GOOSSENS A. – Contact allergy to corticosteroids. Allergy 2000, 55, 698-704.

(6) RIETSCHEL R.L., CONDE-SALAZAR L., GOOSSENS A., VEIEN N.K. – Atlas of Contact Dermatitis. Martine Dunitz, London 1999, 47-55.

.....

Correspondence to:
Goossens An
Department of Dermatology
University Hospital K.U.Leuven
Kapucijnenvoer 33
B-3000 Leuven, Belgium
e-mail: an.goossens@uz.kuleuven.ac.be