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Allergic Contact Dermatitis: a case series and review for the Ophthalmologist

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Summary:

Eyelid dermatitis is most commonly caused by an allergenic response, potentially from exposure at another site, rather than from local toxicity. Yet allergic contact dermatitis (ACD) is a diagnosis often missed by ophthalmologists. We review the literature and detail our experience relating to the causes, clinical features and management of this condition.

Fourteen patients over a 2-year period that were referred to the oculoplastic service for a further opinion, were reviewed in a retrospective, non-comparative study. All patients underwent patch-testing for diagnosis. Eight out of the fourteen patients had delays of greater than 6 months from symptoms to diagnosis. In six of these, this was greater than 1 year. Similar delays are reported in the literature. 79% of our cases were referred by ophthalmologists. Although two of our patients were biopsied, this did not help in making the diagnosis. 13 patients had disease restricted to the eyelids though only five of these had direct contact of the allergen with the eyelids. Two patients were also sensitized to topical steroid creams prescribed for their treatment. All patients improved after removal of the allergen.

Further clinical features and management options from the literature are reviewed and discussed.

Introduction

Causes of an itchy, red eyelid include eczema and psoriasis, seborrhoeic dermatitis, meibomitis/blepharitis and rosacea, dermatomyositis, infections, infestations and malignancy.

Allergic contact dermatitis (ACD) is the commonest cause of eyelid dermatitis. [1-4,6] Whilst many patients never get to the stage of being referred to an ophthalmologist, up to 13% of all patients with ACD have been reported to present with eyelid involvement.[1,2,3] This may be the only affected site and may result in delayed diagnosis.[4,5] Eyelid inflammation tends to be attributed by ophthalmologists more typically, and potentially incorrectly, to local causes, such as topical medications and eye-drops.

Eczema may result from exogenous/endogenous factors. Contact dermatitis is due to exogenous factors and can be irritant or allergic. Irritant contact dermatitis, e.g. toxic reactions to eyedrops, is caused by direct damage and penetration of the skin and represents only approximately 15% of patients with persistent eyelid features.[2,3] On the other hand, allergic contact dermatitis is a delayed type IV hypersensitivity reaction to a specific allergen and accounts for the majority.[2,3,6,7,8] Atopic eczema, which is endogenous, represents only 11-39%. [2,3,9]

Whilst this is well described in the dermatological literature, we believe that ophthalmologists are less aware of the periorbital manifestations and management of this condition. This descriptive study of 14 patients referred to our oculoplastic units for a second/third opinion highlights this delay to diagnosis incurred prior to referral. In addition, we review the current literature and detail the important features of ACD.

Materials and Methods

A retrospective non-comparative case series was performed of patients referred between September 2006 and September 2008 to two specialist oculoplastic centres. 14 consecutive patients with patch-test proven allergens from two independent units were included. The causes, clinical features, management and outcome are described in relation to these patients.

An up-to-date appraised review of the literature was performed, including research from the Ovid Medline and Embase databases. International papers were incorporated. Review articles, large case series and randomised controlled trials were included after appraisal by two separate authors. The main outcome measure was evidence-based literature with clinical relevance.

Results

We studied 14 patients (10 female, age range 5 - 72 years). Eleven patients were referred by an ophthalmologist for a second opinion and the remainder by their general practitioners. Clinical details of each patient are included in Table 1. All patients presented with bilateral upper and lower eyelid involvement, with one exception (Case 10) that had unilateral disease secondary to an eyebrow ring. Most complained of sore, itchy eyelids with swelling of the skin. Some showed lichenification and in two patients (Cases 2 and 6) post-inflammatory hyperpigmentation was the most striking feature. See Figures 1(a-f) and 2(a&b).

The duration of symptoms varied from 2 weeks to 4.5 years (median 1 year, mean 13 months). Eight patients had had symptoms for 6 months or more, of whom five gave a history longer than a year. Many had tried topical emollients and steroids but it was only upon withdrawal of the allergen that their disease improved. All of our patients were referred to a dermatologist for patch testing.

Two important features of our patients are the range and type of allergens involved. These included: quarternium-15, a constituent of shampoo; nail polish resin; nickel; fragrance-mix; balsam of Peru; benzaklonium chloride 0.1% in lubricant eyedrops; house dust mite; tixocortol pivalate, the steroid component found in hydrocortisone, Eumovate, Betnovate and Dermovate creams; and an excipient in Eumovate cream.

Discussion

Eyelid dermatitis is not uncommon; one author[9] reporting involvement in as many as 10% of all general dermatology out-patients. The differential diagnosis includes contact and atopic eczema, seborrhoeic dermatitis, blepharitis, rosacea, psoriasis, dermatomyositis, impetigo and cutaneous T-cell lymphoma.

Acute ACD may present with erythema and macules, papules and/or vesicles. However, blisters are rare on the eyelids. Lichenification, scaling and fissuring are features of more chronic disease. The incidence of ACD as a cause of eyelid dermatitis varies from 29-77% of patients reported,[1,2,3,6,7,8,10] and has been found to be the most likely cause if all 4 eyelids are involved.[10]. It is more common in middle-aged patients with less pigmented skin. Amin, *et al*[11] reported 85.4% of their patients with ACD as caucasian in origin with the greatest prevalence in the 41-70 yr old age-range. Females are most frequently affected (61.8% - 90% of patients) because of use of cosmetics.[1,2,6,7,8,10]

Immune Process

Two stages are necessary in the development of ACD – an initial immune-mediated sensitization to the allergen and then elicitation of the inflammatory response. Sensitization involves penetration of an allergen through the skin and binding to Langerhans antigen-presenting cells. These cells migrate to the lymph nodes and sensitize naïve T lymphocytes, which then relocate themselves back in the skin but throughout the skin. The inflammatory response is elicited by re-exposure to the allergen.

Most environmental allergens are haptens – simple <500d electrophilic molecules that must link to proteins to form a complete antigen before they can sensitize.[12] There are more than 2800 known environmental allergens[13] but not all are haptens. If the hapten complexes with a non-immunogenic carrier, then tolerance is induced, rather than sensitization.[14] The carriers for contact allergens are HLA-DR or class II antigens on the surface of Langerhan's cells.[15]

Because ACD is immune-mediated, compromised immunity is associated with decreased reactivity or anergy. The ageing process modulates ACD, possibly due to a decrease in density of antigen presenting cells and production of proinflammatory cytokines.[16] In addition, children and infants can be affected by ACD. It is unclear when immunocompentence is achieved but patch testing has been performed in infants younger than 2 years of age. [17] More typically, ACD is seen in older children.

Investigation

Skin biopsies are unlikely to distinguish between ACD and other forms of eczema but may help to exclude impetigo and lymphoma. Irritant and allergic contact dermatitis both show spongiosis and a lymphocyte infiltrate. Acute irritant contact eczema usually shows more ballooning degeneration and necrotic keratocytes, whereas ACD shows more spongiosis of the epidermis.[18]

Patch testing is the key investigation used to identify allergens. Frequent contact allergens in eyelid ACD are shown in Table 2. Eyelids are particularly susceptible to ACD because the skin is thinner (thickness of 0.55mm) than on the rest of the face (2.0mm thick). This allows easier penetration of the allergen than at other sites and eyelid dermatitis may therefore be the only manifestation.[11] In addition eyelids may manifest a reaction without direct contact of the allergen at this site.

A thorough history should be taken to identify possible allergens. Details of cosmetics, hobbies and occupation may be relevant. The eyes, eyelids, face and hands (including nails) should be carefully examined.

Patch testing involves application of allergens under Finn Chambers® to the patient's back. Reactions are read at varying intervals. Standard batteries of patch tests, eg. European standard series, TRUE test and North American CD Group (NACDG) series,[19] do not include every relevant eyelid allergen and the test should be adjusted for each patient. Guin (2002) found that 66 out of a total of 167

patients with ACD would have remained undiagnosed if the TRUE test was used alone.[9] Similarly, Katz[4] found that the TRUE test alone would have detected only 37% of ACD allergens and NACDG only 42% of allergens. The most common relevant allergens are the patient's own personal care products.

Whilst patch testing often provides the answer for the patient, interpretation should be performed by an experienced clinician. Untrained interpretation exposes the patient to incorrect over and under-testing, deceptive results and potentially unwanted sensitization. Interpretation involves being able to separate irritant and allergic reactions, determining the relevance of the antigen and the optimum reading time and appreciation of cross-reactions and co-reactivity.

False positives can occur if the allergen causes an irritant rather than allergic response. The test may need to be repeated with the allergen at a lower concentration. In addition, even if a chemical is found to be allergenic it cannot be assumed that it is causative. The relevance of the antigen is important. A provocation test or repeat open application testing (ROAT) may be necessary. This involves the patient applying the commercial product to normal skin several times daily for 1-2 weeks.[20]

Most false negative responses can be avoided by performing a second reading of the test sites 48 hours after the first one. Some studies advocate readings at 4-7 days, especially in elderly patients, to ensure any allergic response is elicited.[21,22] Neomycin reactions may take longer – one study showed that half are not evident until 96 hours.[23] In addition, if too low a concentration is used in testing, sensitization may not occur. Sensitization is dependent on dose of chemical per unit area of skin (up to a limit of 0.1cm2).[24] Concentrations of ophthalmic preparations may need to be tested at a higher level due to difficultly in penetrating the skin on the back.[25]

Side effects of patch testing include a severe local reaction or flare reaction at a distant site, an "angry back/excited skin" syndrome where numerous positive reaction occur, pigment changes, scarring and

keloids, infections and potentially anaphylaxis. [26] For all of these reasons, patch testing should be performed by an experienced dermatologist. .

Treatment

It is well established that patients may occasionally continue to have symptoms even after avoidance of the allergen.[27,28] Treatment for symptom relief is therefore required in addition to simply identifying responsible allergens.

Treatment should include emollients, treatment of secondary infection if present and down-regulation of the immune response. Topical anti-pruritics should be avoided because of the risk of secondary sensitization.[29]

Glucocorticosteroids are usually the primary choice for immune modulation and their effective treatment of ACD is well documented.[30,31,32] Inflammation is reduced by suppressing the recruitment of polymorphonuclear leukocytes and reversing capillary permeability. Topical steroids are usually sufficient and treatment should be limited to 2-3 weeks duration. Low potency steroids such as hydrocortisone and desonide are safer on the face, though stronger steroids such as clobetasone proprionate or betamethasone diproprionate are used for moderate-severe disease.[33] Longstanding application of topical steroids is associated with skin atrophy, telangiectases and acneiform reactions. If more than 20% of the body surface area is involved, or if there are bullae or extensive facial involvement, then treatment should be considered with systemic steroids.

It is important to be aware that topical steroids may themselves be allergenic, as seen in case 12. One study[34] of 31 patients with ACD that had worsened or shown no response to topical corticosteroid treatment found that 22% had a positive patch test result to the steroid itself. In other studies,[35,36] the steroid has been implicated in 0.2-5%.

Ascomyscins such as tacrolimus (TK506) (Protopic oinment 0.03% or 0.1%) and pimecrolimus (ASM 981) (Elidel cream) have recently been introduced as treatment options and provide a solution for thin-skin areas, eg. the face and eyelids. [37,38] They are topical calcineurin inhibitors and cause a reduction in interleukin, leukotriene, histamine and serotonin release, thereby effectively suppressing the immune response.[29,39] Both agents target the human epidermal Langerhans cell[40] and have been shown to inhibit the elicitation phase of ACD in a mouse model.[41] In addition, a study in humans found that tacrolimus also suppresses the sensitization phase.[42] Tacrolimus ointment at concentrations of both 0.03% and 0.1% has been found to be an effective treatment for nickel-induced steroid resistant ACD in adult and paediatric patients. Safety and efficacy of usage has also been reported in children of two years or older.[12] A 0.1% concentration is probably more effective[43,44,45] but is more frequently a cause of itching and burning. These rapidly decrease after the first week of treatment. Although Cyclosporin A is also a successful calcineurin inhibitor, it has limited penetration through the epidermis and limited topical application for this condition. [30, 46, 47]

Ascomycins have been compared with topical steroids. A small double-blind RCT pilot-study[48] examining nickel ACD looked at 4 treatment groups - pimecrolimus 1% cream, tacrolimus 0.1% ointment, clobetasol 0.05% ointment, triamcinolone 0.1% ointment - and two control groups of topical vehicle application. No statistically significant differences were found between any of the groups, although the treatment groups showed a clear trend towards being more effective than control. However, Saripalli et al[49] induced nickel ACD in patients and found that tacrolimus was significantly more effective than vehicle. Alomar et al[50] corroborated this finding. Similarly, pimecrolimus at 0.2% and 0.6% formulations has successfully treated nickel-induced ACD.[51]

Other treatments options for more widespread disease away from the eyes, patients that are unresponsive to the above treatments, or for those who cannot avoid the provoking factors include phototherapy – PUVA (oral psoralen photochemotherapy) and shortwave UVB light. In addition, use

of Grenz rays[52] and systemic immunosuppressants[53] such as azathioprine and mycophenolate mofatil have been described in ACD.

In our study, all of the patients improved with removal of the allergen with/without a short course of topical immunosuppressants.

In conclusion, eyelid dermatitis may be the only dermatological manifestation of ACD. (See summary table3). Delay in diagnosis commonly hinders appropriate treatment and avoidance of allergens. In our experience, marked delays were due to lack of awareness of the condition by referring ophthalmologists. Improved awareness is essential. In addition, it should be remembered that the corticosteroids used to treat ACD may in fact be causative themselves, and patients who are unresponsive to treatment ought to have corticosteroids included as potential allergens in their patch testing.

Legends to Figures

1a-c: These images correspond to Case 4 in the series who was found allergic to her nail polish. Note the bimedial upper and lower lid erythema and thickening. Examination of her fingernails revealed periungual vesiculation (1c).

1d-f: Images 1d and 1e show another patient from our case series with the typical bimedial upper and lower lid erythema in a 'butterfly' distribution. 1f: Histology specimen from the same patient (H&E stain, x10 magnification). Lichenification, hyperkeratinization, non-specific generalized inflammatory cell infiltate and a thickened cornea stratum are seen.

2a: This patient was referred by an ophthalmologist for upper blepharoplasties, but ACD was found to be causative. Bilateral upper lid erythema is clearly visible in this photo.

2b: This patient demonstrates subtle features of eyelid 'eczematous' dermatitis and medial lower lid ectropion can also be seen. This clinical appearance had prompted repeated prescriptions of steroid cream treatment prior to his presentation to our unit. He was found patch test positive to Eumovate cream.

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Table 1 - full details of our case series

Case	Age (years)	Clinical Features	Symptoms to diagnosis	Patch Testing Positive Results	Management	Outcome
1	46	Sore, itchy upper and lower eyelids with erythematous scaling and thickening medially in butterfly pattern. No benefit with steroid/anti-fungal creams/emollients.	1.5 years	Quarternium-15, nickel sulphate, caine mix, formaldehyde, colophony, methylchloroisothiazolinone and methlisothiazolinone, L'Oreal Cleansing Experience, Lancome Teinte SPF 15.	Cessation of shampoo, moisturizer and make-up products containing allergens. Reducing regime of Betnovate ointment od 2 days, Betnovate RD od for 3 days, then 1% hydrocortisone od.	Dramatic improvement within 1 month
2	20	Bilateral periocular dermatitis with cicatricial medial ectropion. Inner canthal skin lichenification. No resolution with steroid ointments or moisturizers to the skin.	4.5 years	Aerosol fragrance-mix	Avoidance of allergen, regular emollients, Betnovate and Eumovate cream.	Periorbital eczema and entropion resolved
3	74	Itchy eczematous dermatitis of eyelids, mild eczematous changes to cheeks and behind ear.	9 months	Caine mix, fragrance mix, nickel and carba mix, E45 itch relief cream, Eumovate (no reaction to Diprobase/hydrocortisone)	Avoidance of allergens, Diprobase ointment to wash and moisturize tds, hydrocortisone ointment 0.5 – 2.5% depending on redness.	Clinically much improved within 2 months
4	45	Bilateral, itchy, asymmetric erythematous eyelids. No other dermatitis elsewhere on body/face except periungual vesicles on fingers.	2 months	Nail polish; toluene-sulfonamide formaldehyde resin	Changed to "hypoallergenic" polyester resin nail polish, 1% hydrocortisone ointment tds to eyelids.	Complete resolution within 2 weeks.
5	72	Mild intermittent erythema and eczematous eyelid changes.	1 year	Apitol, chloroethylene and ethylene diamine	Stopped mascara wear. No response to Elidel 1% or hydrocortisone 1% use. Tacrolimus 0.3% given.	Resolution of symptoms within 1 month
6	50	Episodic eyelid rashes, puffiness and skin darkness.	1 year	Nickel, fragrance, balsam of Peru and imidazolidinyl urea preservative	Avoidance of allergens.	Complete resolution
7	49	Eyelid puffiness, episodic itchy erythematous eyelid skin. Occasional neck rash.	3 years	Methylchloroisothiazolinone and methlisothiazolinone, from shampoo and her Crème de la Mere foundation	Avoidance of products.	Improved within 2 months

Table 1 - full details of our case series (continued)

Case	Details	Clinical Features	Symptoms to diagnosis	Patch Testing Positive Results	Management	Outcome
8	56	Bilateral periocular dermatitis, itchy lids with some lichenification.	4 months	Fragrance-mix	Ceased aftershave lotion, hydrocortisone 1% ointment tds to eyelids.	Resolved within 4 weeks
9	61	Periocular dermatitis and bilateral conjunctival inflammation since starting ocular lubricants.	2 weeks	Benzalkonium chloride 0.1%aq.	Topical lubricants stopped, predsol 0.5% qds both eyes and topical hydrocortisone 1% tds to eyelid skin.	2 week resolution
10	23	Left-sided eyelid and eyebrow dermatitis, following insertion of eyebrow ring.	4 weeks	Nickel	Removal of piercing, 0.1% betamethasone valerate ointment bd.	Complete resolution
11	5	Bilateral lichenified itchy eyelids.	6 months	House dust mite	Measures to decrease exposure (mattress/pillow protectors, cleaning of floors, open windows daytime, washing stuffed toys etc.). Topical hydrocortisone 1% tds to skin.	Partial resolution over 2 months
12	52	Bilateral upper and lower eyelid erythema and oedema. Failed treatment with hydrocortisone 1% ointment.	14 months	Tixocortol pivalate (found in hydrocortisone, Eumovate, Betnovate and Dermovate ointments), quaternium-15	Avoidance of allergens.	Full resolution within 2 months
13	50	Bilateral upper lid erythema – referred for consideration of blepharoplasties.	6 months	Parabens and lanolin	Avoidance of face creams. Reducing regime of hydrocortisone 1% ointment.	Complete resolution
14	28	Sore, itchy, erythematous upper and lower eyelids.	1 year	Nickel sulphate	Avoidance of her eyelash curlers. No topical creams necessary.	Complete resolution

Table 2 – Common contact allergens particularly relevant to eyelid ACD

Allergen	**Source**
Gold sodium thiosulfate 0.5%	Jewellery / metal
Fragrance and preservative	Cosmetics, shampoos, soaps, moisturizers, lotions
Nickel	Jewellery, eyelash curlers, traces in make-up
Thiuram mix	Rubber of eyelash curlers
Cocamidopropyl betaine 1% (CAPB), Amidoamine 0.1%, Quarternium-15 2%	Preservatives and surfactants in shampoos
Tosylamide formaldehyde resin	Fingernail polish, adhesives, glues, bonding agents
Neomycin	Topical medications
Benzalkonium chloride	Topical medications, face washes, hand scrubs, cosmetics
Dust mites or animal dander	Make-up brushes

Table 3 - Summary Table

Recommended 4-step Approach to Management of Suspected ACD		
1	History	Ask about known allergens, types of cosmetics, occupational and leisure pursuits. Remember allergens may not necessarily be those in direct contact with the eye.
2	Examination	Eyelids and nails – may not have localized nailbed changes. Check for artificial nails.
3	Refer for patch testing	Standard patch testing batteries should be supplemented with patient's own cosmetics or particular allergens from history. Allow 48-96 hours prior to result reading.
4	Treatment	Cessation of allergen contact. Symptom relief – emollients, topical antipruritics, oral antihistamines. A 2-3 week course of topical steroids or tacrolimus/pimecrolimus use.

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