

Donatella SCHENA
Francesca FANTUZZI
Giampiero GIROLOMONI

Sezione di Dermatologia e Venereologia,
Dipartimento di Scienze Biomediche e
Chirurgiche, Università di Verona, Piazzale
A. Stefani 1, 37126 Verona, Italy

Reprints: D. Schena
<donatella.schena@azosp.vr.it>

Contact allergy in chronic eczematous lip dermatitis

Chronic eczematous cheilitis comprises a heterogeneous group of disorders, the cause of which often remains obscure. Our object was to investigate the frequency of contact allergy in a cohort of patients with chronic eczematous cheilitis attending a tertiary referral clinic. Patients (106 females and 23 males) with chronic eczematous cheilitis were analyzed retrospectively. All patients were tested with a standard patch test series and a fraction with a dedicated patch test series. Children were also tested with atopy patch tests. Moreover, all patients were investigated for past or current presence of atopic diseases. Patch-test reactions of possible or probable relevance were detected in 84 patients (65.1%; 72 females; median age 40), of uncertain or not relevant significance in 26 (20.1%) and negative in 19 (14.7%). An extended series was necessary to reveal hapten hypersensitivity in 42 patients. The most frequent causes of allergic cheilitis were nickel, fragrances, balsam of Peru, chromium salts and manganese salts, present primarily in cosmetics, dental materials and oral hygiene products. Twenty four patients (18 females; median age 21; 18.6%) were diagnosed as having atopic dermatitis of the lips. Four children had allergic contact cheilitis to haptens or food allergens, whereas six had atopic cheilitis. Twenty one cases (16.3%) were considered irritant contact cheilitis. Allergic contact cheilitis is common in adult patients, with the haptens responsible varying with age. Patients with chronic eczematous cheilitis should undergo extended patch testing.

Key words: allergic contact dermatitis, atopic dermatitis, cheilitis

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Cheilitis refers to an inflammatory process that affects the lips, including the cutaneous side, the vermilion border and/or the lip mucosa. The majority of cases of cheilitis affect the skin and vermilion border, as the oral mucosa is less affected by inflammatory and allergic reactions [1, 2]. Indeed, it is possible that substances contacting the mucosa more easily induce tolerance rather than immunogenic responses [2]. Chronic eczematous reactions account for most cases of chronic cheilitis, but it is sometimes difficult to establish the nature and cause of the reaction. Apart from single case reports or small case series, only a few studies on larger patient populations have been performed to define the origins of chronic eczematous cheilitis [3-6]. In many cases, chronic cheilitis is the result of an allergic reaction to small molecular weight chemicals known as haptens, or more rarely to protein allergens (allergic contact cheilitis, ACC) [7]. In other cases, it derives from the direct toxic action of contacting substances (irritant contact cheilitis, ICC), or from an intrinsic propensity to develop inflammatory responses to minimal stimuli, such as in atopic cheilitis. The diagnostic work up of chronic eczematous cheilitis encompasses allergy testing with standard and, frequently, extended patch test series to confirm or exclude the involvement of an allergic component.

The objective of this study was to define the frequency of contact allergy and atopy in relation to age and the site involved in a cohort of patients with chronic eczematous cheilitis. The results show that ACC to cosmetics and dental material is the most common form in adult patients. Children suffer from both atopic cheilitis and ACC to haptens and food proteins. Elderly patients have ACC to cosmetics, dental material and topically applied drugs.

Patients and methods

This was a retrospective study carried out from January 2001 to December 2006. It involved the examination of 129 Caucasian patients referring to our Contact and Occupational Dermatoses Clinic who presented with eczematous lesions on the vermilion border, the nearby skin or the lip mucosa. Inclusion criteria were the presence of eczematous lesions for at least 3 months and the execution of standard patch tests. Patients with lichenoid reactions of the lips or the oral mucosa, orofacial granulomatosis, swelling, burning or soreness of the lips but no lesions, were not included. Demographic data, disease history, patients' work details, cosmetics and medications applied on the lips, dental

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Table 1. Patch test with cheilitis series used

Benzoic acid 5% pet.	Oleyl alcohol 30% pet.
Cinnamic aldehyde 2% pet.	Aluminium chloride 2% aq.sol.
Anethole 5% pet.	Azulene 1%
Benzalkonium chloride 0.1% aq.	Benzoin 10% alc.
Carvone 5%	Beeswax 30% pet.
Chloroacetamide 0.2% aq.sol.	Dichlorophene 1% aq.sol.
D&C red 21 (Eosin)	Hexylresorcinol 1% pet.
Eugenol 5% pet.	Phenyl salicylate 1% pet.
Ethylene glycol 5% alc.	Isoeugenol 5% pet.
Limonene R 2% pet.	Limonene S 2% pet.
Menthol 1% pet.	Octylmethoxycinnamate 7.5% pet.
Benzophenone 3 5% pet.	Eucalyptus oil 1% alc.
Laurel oil 2% pet.	Cinammon oil 2% pet.
Peppermint oil 1% pet.	Rosemary oil 5% alc.
Spearmint oil 2% pet.	Propyl gallate 1% pet.
Propolis As is	Quaternium-15 2% pet.
Sodium benzoate 5% aq.sol.	Sodium lauryl sulfate 1% aq.sol.
Thymol 1% pet.	Vanillin 10% pet.
Castor oil As is	Ricinoleic acid 30%
D1-alpha-Tocopherol 20%	Chlorhexidine digluconate 0.5% aq.
Platinum chloride 1% aq.sol.	Manganese chloride 2% pet.
Palladium chloride 1% pet.	Zinc chloride 2% aq.sol.
Sorbitan monooleate 5% o.o.	Butylhydroxyanisol 1% pet.
butylhydroxytoluene 1% pet.	D&C orange 17 (C.I. 12075) 2% pet.
D&C Orange 4 (CI 15510) 2% pet.	D&C red 11 (C.I. 15630) 2% pet.
D&C Red 17 (C.I. 26100) 2% pet.	D&C red 36 (C.I. 12085) 2% pet.
D&C Red 22 50% pet.	Yellow orange S yellow 6 pet.
D&C Yellow chinoline 2% pet.	Yellow tartrazine – yellow 5 pet.

Alc.: alcohol 70%, Aq.: aqueous, As is: undiluted, c.o.: castor oil o.o.: olive oil, pet.: petrolatum, sol.: solution.

hygiene habits, co-morbid diseases, systemic medications and physical findings were registered. Personal and family history of atopic disease (asthma, atopic dermatitis and allergic rhino-conjunctivitis) and past skin reactivity or serum specific IgE to common allergens were noted. All the patients were patch tested with the standard series (Firma, Florence, Italy) elaborated by the Italian Society of Allergological, Occupational and Environmental Dermatology (SIDAPA series)¹. Forty-two patients were also investigated with a patch test cheilitis series elaborated by us (*table 1*), which was used whenever the standard patch test was negative or gave irrelevant positivity. This test series was created utilizing the specific cheilitis battery proposed by Firma, integrated with the most frequent haptens responsible for ACC reported in the literature. Finally, 10 patients were tested directly with the suspected products, such as toothpastes, lip-balms and lipsticks. To do this, the product was applied directly on the skin using Haye's test chambers and left in place for 2 days, as previously reported [12]. Positive reactions observed by testing patients' own products have been validated by executing stop-restart tests with the same product. Children (≤ 14 years) were also investigated with the atopy patch tests for house dust mite, latex, pollens and foods (Alk-Abelló[®], Hørsholm, Denmark) [8]. Patch tests were carried out with Haye's test chambers

applied on the back and left in place for 2 days. Readings were taken after 48 and 96 hours, and scored according to the recommendation of the International Contact Dermatitis Research Group [9, 10]. Positive reactions were defined as relevant whenever the patient was exposed to an allergen during episodes of cheilitis and cheilitis improved or disappeared when the exposure ceased.

Results

A total of 129 patients referring with chronic eczematous cheilitis were included in the study. They were 106 females and 23 males, aged from 4 to 81 years (mean age, 42; median age, 41). Lesions exclusively affected the vermilion border in 58% of cases or the lip skin in 33%, both these locations in 7%, and the vermilion border and the lip mucosa in only 2% of patients. Cheilitis lasted from 3 to 72 months, with a mean and a median duration of 35.2 and 12 months, respectively. There were no substantial differences in disease duration between the different classes of age. Most patients referred subjective symptoms such as pruritus, burning or pain.

Positive patch test reactions were considered of possible or probable relevance in 84 patients (65.1%; 72 females and 12 males; median age 40), but the use of the extended series was necessary to reveal relevant hypersensitivity in 42 patients. Fifty-four patients developed relevant reactivity to

¹ www.sidapa.com

Table 2. Number of patients with positive and relevant patch test reactions

	Positive patch test	Relevant patch test		Positive patch test	Relevant patch test
Metals	37		Preservatives/antioxidants	22	
Nickel sulphate	20	10	Kathon CG	4	2
Potassium dichromate	6	3	Formaldehyde	3	0
Manganese chloride	4	3	Thimerosal	3	0
Cobalt chloride	4	0	Benzalkonium chloride	2	1
Gold sodium thiosulphate	2	2	Euxyl K 400	2	2
Palladium	1	1	Hexylresorcinol	2	1
			Propyl gallate	2	2
Fragrances/flavouring agents	25		Tocopherol	2	0
Fragrance mix	10	9	Imidazolidinylurea	1	0
Balsam Perù	8	8	Sodium lauryl sulphate	1	1
Limonene R e S	3	3			
Benzoin	2	0	<i>Drugs</i>	5	
Menthol	2	1	Neomycin sulphate	5	5
Pepper mint oil	2	2			
Eucalyptus oil	1	1	<i>Product as it is</i>	3	
			Toothpaste Acquafresh	1	1
Miscellaneous	19		Toothpaste AZ carie	1	1
Colophony	4	1	Neutrogena labbra	1	1
Lanolin	3	2			
Beeswax	2	2			
Propolis (resin)	2	1			
Toluenesulfonamide	2	1			
formaldehyde resin					
Castor oil	1	1			
Propylene glycol	1	1			
Red 17 (dye)	1	1			

a single hapten, whereas 28 patients had multiple sensitivities; two subjects had negative patch testing but developed positive reactions to products tested as such (lipsticks and toothpastes). *Table 2* lists the number of patients reactive to each hapten. Among the relevant reactivities, the most commonly involved were metals, fragrances and preservatives, present primarily in cosmetics, but also in dental materials and oral hygiene products. Among patients with positive patch tests, 40 (49%) also had a history of atopic diseases (atopic eczema, asthma and/or rhino-conjunctivitis). They were mostly adults aged from 20 to 60.

Patch tests were positive but of uncertain or not relevant significance in 26 (20.1%) and negative in 19 (14.7%). Of these patients, 24 (18.6% of total patients) were diagnosed as having atopic dermatitis of the lips, since there was a personal history of atopic dermatitis elsewhere (38%), asthma (10%) and/or rhino-conjunctivitis (7%), and at least one determination documenting skin or serum allergen specific IgE. However, only two of these patients had concurrent atopic dermatitis lesions and atopic cheilitis at the

moment of the visit. Finally, the 21 patients (16.3%) with either negative (n. 19) or irrelevant positive patch tests (n. 2), as well as no past or present history of atopic diseases, were diagnosed as ICC. In the majority of patients with ICC, the disease was associated with the use of cosmetics or hygiene products. Separating patients according to age range, four classes could be identified (*table 3*). ACC was more common in adult and aged patients, whereas atopic cheilitis was the predominant form in children, but it was also observed in adults. All the children were investigated with atopy patch tests and all eight atopic children gave positive reactions to food, but with uncertain significance in six. In contrast, two atopic children had ACC to food allergens (egg and shellfish respectively). *Table 4* shows that the sources of allergens vary in relation to the patients' ages. Cosmetics were the most common cause in adults whereas dental materials and oral hygiene products were common in all age groups. In elderly patients topical medicines (neomycin) accounted for a relevant proportion of positive reactions (21%).

Table 3. Different age classes of patients with chronic eczematous cheilitis

	0-14 years (n = 10)	15-40 years (n = 51)	41-60 years (n = 46)	> 60 years (n = 22)
Allergic contact cheilitis	4 (40%)	37 (72.5%)	24 (52.2%)	19 (86.4%)
Atopic cheilitis	6 (60%)	11 (21.6%)	5 (10.9%)	2 (9.1%)
Irritant contact cheilitis	-	3 (5.9%)	17 (36.9%)	1 (4.5%)

Table 4. Allergic contact cheilitis and sources of allergens in different age classes of patients with chronic eczematous cheilitis

	0-14 years (4/10)*	15-40 years (37/51)*	41-60 years (24/46)*	> 60 years (19/22)*
Cosmetics	-	23 (62%)	14 (58%)	5 (26%)
Dental materials	1 (25%)	6 (16%)	4 (17%)	6 (32%)
Oral hygiene products	1(25%)	8 (22%)	5 (21%)	4 (21%)
Medicines	-	-	1 (4%)	4 (21%)
Foods (egg, shellfish)	2 (50%)	-	-	-

*Number of patients with ACC on patients with chronic eczematous cheilitis.

Discussion

Lips can be affected by a large variety of inflammatory disorders, including lichenoid reactions, lupus erythematosus, orofacial granulomatosis, urticaria. Chronic eczematous cheilitis is the commonest form, and manifests with erythema, dryness, scaliness, fissuring and is often accompanied by angular lesions (*figure 1*). Females are more frequently affected than males, as confirmed in our study, where we observed a F:M ratio of 4.6:1, a predominance that can be explained by the presumption that women use more cosmetics and lip products than men and are also more likely to seek medical attention for a process affecting physical appearance. The nature and causes of chronic eczematous cheilitis can be diverse, but most cases can be defined as of allergic, irritant or atopic origin. The prevalence of ACC remains uncertain, and only a few studies of sufficient size have investigated this issue. In these studies the prevalence of ACC among patients attending a tertiary referral center varied from 15% to 34%, whereas ICC and atopic cheilitis represented 5-37% and 19-33%, respectively [3-6]. In our series, ACC was diagnosed in 65% of patients, whereas ICC and atopic cheilitis accounted for 16.3% and 18.6%, respectively. The higher percentage of patients with ACC and lower percentage of ICC in our study may be related to the higher selection of patients attending our Clinic. Indeed there are no studies investigating the prevalence of ACC and other eczematous cheilitis in the general population. ACC was more common in adults



Figure 1. A) allergic contact cheilitis to oral hygiene products (menthol); B) irritant contact cheilitis in a female patient; C) allergic contact cheilitis in a young patient bearing a metallic device (nickel sulphate); D) atopic cheilitis in a child.

and rarely observed in children. The main causes of ACC were cosmetics, such as lipsticks [3, 4, 6], oral hygiene products [4, 12], dental materials [13, 14], nail cosmetics, and, more rarely, foods [15], and these data have been confirmed in our case series. Metals, fragrances, and preservatives were the most relevant haptens contained in cosmetics and oral hygiene products. Metals were most likely the relevant haptens present in dental materials. Other than nickel, manganese and cobalt reactivity was detected in some patients, in all cases together with nickel. The relevance of dental material was established by the disappearance or marked improvement of cheilitis upon material withdrawal, but we did not address the role of each individual metal [13, 14]. Also, we did not test for acrylates and methacrylates, as these substances are very rarely involved in cheilitis [13, 14]. Patch tests with extended series or with the product as is was required to establish the cause of ACC in about half and in three patients, respectively. These results confirm the necessity to consider a wide range of possible substances before excluding the allergic nature of the cheilitis, and thus the importance of using extensive patch test series [16, 17]. Taking into account different age groups, cosmetics were found to be the most frequent cause of ACC in adults, whereas dental materials and oral hygiene products were common in all age groups. Topical medicines (neomycin) seemed to be a relevant cause of ACC only in the elderly, where they accounted for a relevant proportion of reactions (21%). Atopic cheilitis was diagnosed in less than 20% of our patients, a percentage that is in the lower range of previous studies [3-6], possibly because patients with atopic dermatitis in typical areas were not included in the study. Indeed the lips are commonly involved in patients with atopic dermatitis. Diagnosis may be instead more difficult when the patient comes with eczematous lesions limited to the lips. In such case a careful history, the presence of specific IgE, and the absence of hapten patch test reactivity help in the diagnosis. A number of reports analyzed patch test reactions to protein allergens in patients with atopic eczema, but no definitive conclusion about the relevance of these tests can be drawn at the moment [8, 11, 18]. Only ten children were included in our study, with eight showing a positive patch test reaction to foods. However, the reaction was interpreted as relevant only in two (shellfish and egg), where avoidance led to disease resolution, and re-challenge to disease reappearance. At any rate, the number of children included in our study was too low to draw any conclusion on the importance of food allergy in cheilitis. Two additional children had ACC to haptens. The anatomical sites involved seemed not to be related to the type of eczematous cheilitis and, in the case of ACC to the source of hapten, in line with previous results [19].

Conclusion

Chronic eczematous cheilitis may be of disparate nature and attributed to different factors. Patch testing is essential for investigating a suspected contact cheilitis, and extended patch test series and/or testing with the patient's personal products is very important to definitively establish the causative substance. Atopy is very common in the population, including patients with cheilitis, and thus the atopic nature of the symptoms should be precisely defined. ■

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