

RISK OF ALLERGY TO FOOD PROTEINS IN TOPICAL MEDICINAL AGENTS AND COSMETICS

F. Codreanu (1), M. Morisset (1), V. Cordebar (1), G. Kanny (1), D.-A. Moneret-Vautrin (1)

The risk of allergy to food proteins in cosmetics and topical medicinal agents is poorly evaluated. IgE dependent contact urticaria and contact dermatitis are observed. Eleven cases (7 infants and 4 women) are reported. Wheat, egg, oats, milk, peanut proteins are incriminated by prick-tests or atopy patch-tests. Cases are related to a previous food allergy and other ones may indicate primary sensitization to topical creams mainly used for skin care of atopic dermatitis. A consecutive exercise induced anaphylaxis to wheat and a long lasting sensitization to wheat have been observed. A clear and accurate identification of food allergens in cosmetics and topical agents is necessary. Given the hyper-permeability of infant skin, topical products containing food proteins of known allergenicity are contra-indicated for neonates, and for infants with atopic dermatitis, which may be associated with skin hyper-permeability.

Allergy - Food proteins - Skin care - Cosmetics - Infancy - Adults.

INTRODUCTION

The risk of allergy to food proteins in cosmetics and topical medicinal agents is poorly evaluated. Several cases of contact allergy have been reported in the literature and are mainly cases of contact dermatitis, eczema or atopic dermatitis (AD) and contact urticaria. The contact allergy usually occurs with cosmetics and skin care products used to treat AD in infants, but there are also isolated cases of allergy to topical medicinal agents. Against the background of cases treated in our department, we propose a review of the literature of contact allergy to food proteins in topical agents whose most frequent allergens are wheat proteins and hydrolysates, oats, milk, sesame, as well as peanut, almond and egg.

FOOD PROTEIN LABELLING REGULATIONS FOR TOPICAL AGENTS

The first French (1) and European (2) regulations concerning the labelling of cosmetics date from 1975. They aimed to protect users from serious risk of toxicity, but did not tackle allergy-related problems. In 1996, the European Community first drew up a list of cosmetics (3) together with an International Nomenclature of Cosmetics Ingredients (INCI) containing non-proprietary names that had to appear on the

(1) Service de Médecine Interne, Immunologie Clinique et Allergologie - Hôpital Universitaire de Nancy - 54035 Nancy.

label. It was only in December 2000 that this regulation was applied in France, thus making manufacturers and authorities responsible for Marketing Authorizations, as well as cosmetic importers, aware that it was mandatory to identify ingredients by their INCI name on the labels. The latest list of cosmetics was drawn up by the European Community in 2003 and it mentions 240 proteins with various properties, some of which are used in food: skin care and protection, emollients, emulsifiers, hair conditioners, etc. Some proteins are of vegetable origin: peanut, lupin, soya, wheat and its hydrolysates, oats, sesame. Others are of animal origin: egg, cow milk, casein, fish extracts. The cosmetics industry also uses many vegetable oils and protein hydrolysates. A medicinal product is composed of an active substance and excipients that may contain food proteins. A European directive from 2003 (4) makes it mandatory for the labels of oral and injectable medicinal products to list all excipients with known effects. In topical agents, all ingredients must be identified on the outer packaging. Although food proteins appear to be well documented on labelling, we shall see that it is sometimes difficult to identify a food allergen clearly and accurately.

ALLERGIC REACTIONS TO FOOD PROTEINS IN COSMETICS AND TOPICAL MEDICINAL AGENTS

Two types of reaction are possible in the event of allergy to food proteins applied to skin: immediate hypersensitivity (contact urticaria and exceptionally

anaphylactic shock) and late hypersensitivity reactions. Contact dermatitis embraces both immediate and late reactions.

Sensitization to food proteins found in topical agents usually occurs in atopic subjects and may be followed by food allergy. Patients with AD and neonates are more likely to be sensitized to food allergens via the skin.

Contact allergy to wheat protein is the commonest. The first cases date back to the time when infants with AD were treated with wheat starch baths. We noticed several cases of skin rash in infants after these baths with later evidence of sensitization to wheat flour. Assays of residual wheat proteins in wheat starch have been carried out on foods guaranteed to be gluten-free for consumption by patients with celiac disease (5). There were slight traces of residual gluten ranging from 20 to 200 ppm. Even if this amount corresponds to a daily gluten intake of 30 mg/day, and even if this amount of residual wheat protein is not harmful to patients with celiac disease, this is not the case for infants allergic to wheat flour, since small amounts of wheat proteins are applied daily to damaged, permeable skin for several months.

We report a case of generalized erythema in a 50-year old woman after use of a shower gel containing wheat. She had confused shower gel with body cream and had left the shower gel on her skin for 24 hours. Two explanations were possible: irritation dermatitis following the abnormally long application of the shower gel, and contact allergy to wheat proteins in the shower gel. It is interesting to note that after this skin reaction, she presented with two episodes of exercise induced anaphylaxis, that was related to the ingestion of wheat, a sensitization to wheat being confirmed by prick-tests.

The following cases are contact allergies to wheat protein hydrolysates and concern women using cosmetics. Wheat hydrolysates are obtained by acid, alkaline or enzymatic hydrolysis of wheat germ, mainly gluten. They are frequently found in cosmetics since they have various anti-static, hair conditioning and skin care properties. A 17 y.o woman developed contact eczema after using Bonacure Repair Schwarzkopf® shampoo that contained a wheat hydrolysate. The prick-test was positive to the shampoo: 5 mm (codeine control 2 mm). The second woman exhibited a facial angioedema with generalized urticaria after application of a mascara from Sothys® that also contained wheat hydrolysates. The prick-test was strongly positive (fig 1). The two patients had previous food allergy to wheat.

The first cases of contact allergy to protein hydrolysates in hair conditioners were reported in 1990 (6). In 1998, Niinimäki (7) carried out a large-scale prospective study on skin sensitization (prick and patch-tests) to 22 protein hydrolysates in more than 2,000 patients

divided into three groups (contact dermatitis in hairdressers, atopic patients sensitized to airborne allergens and patients with atopic dermatitis). Prick-tests were often positive for a collagen protein hydrolysate, crotein Q, responsible for three cases of contact urticaria and one of conjunctivitis. Skin test reactions to milk and wheat hydrolysates were all negative. In 2000, Sanchez-Perez (8) described the first case of contact dermatitis in a non atopic woman due to a cosmetic cream containing wheat protein hydrolysates that was applied daily for two years. The same year, Varjonen (9) reported another case of contact dermatitis in an atopic hairdresser with contact eczema to latex that persisted despite eviction, and attributable to wheat hydrolysates in the shampoo used on customers (positive prick-test and wheat flour specific IgE). Eviction of this type of shampoo resulted in complete regression of symptoms. These two cases occurred in people tolerant to wheat. Two cases of contact urticaria were found in the literature; the first (9) due to a moisturizing cream where the allergy report revealed a prick-test positive only to wheat hydrolysate with no sensitization to wheat flour. The author suggested the hypothesis of neo-allergenicity of wheat hydrolysates. The second case of contact urticaria due to moisturizing cream (10) was particularly interesting since the patient later developed food allergy to wheat flour. Does skin allergy to wheat

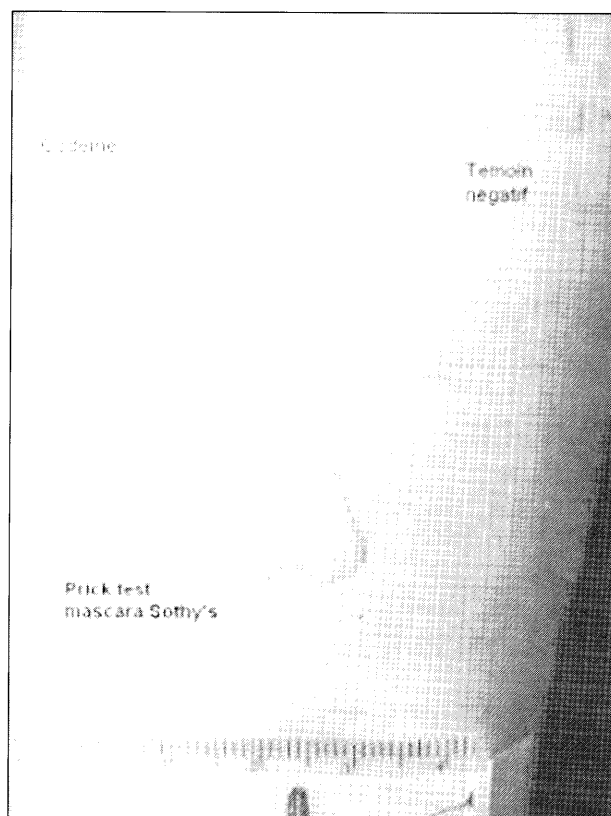


Fig. 1: Prick-test to mascara (case report 4).

hydrolysates favour onset of food allergy to wheat? This case report suggests that contact allergies to wheat hydrolysates occurred in three distinct conditions: isolated contact allergy (local phenomenon), previous sensitization to wheat flour, later development of food allergy to wheat.

Another frequent contact allergy is linked to oat proteins. Skin care products for infants with AD often include oats for their emollient, anti-pruriginous and anti-inflammatory properties. We report a case of progressive lesions of AD after application of a cream containing oat milk, Aderma®, on a 4-month old infant with AD and allergy to cow's milk. Positive patch-tests (++) confirmed the sensitization to oats and showed a sensitization to wheat, that the child had never ingested. The hypothesis of *in utero* wheat sensitization cannot be discarded but most likely, the infant sensitized to oats through Aderma® and then developed a cross-sensitization to wheat. At the age of one year, the child had identical results for the patch-test to wheat and remained on an eviction diet. Several cases of eczema in children with AD are reported in the literature; three after oatmeal baths (11); four after application of an oatmeal based emollient cream (12). One case of contact urticaria was reported in a 7-year old girl with AD after using Dermalibour®, an anti-bacterial cream containing oat extract (13).

Milk proteins are also at risk. We report two cases of contact urticaria, after application of a gulf balm, Gencifrice®, containing lactoserum proteins (case 7), and after using liquid soap containing micronized milk, Saugella® (case 8). The prick-test to soap was positive (8 mm) (fig. 2) whereas the prick-test to native milk produced a 5 mm wheal. Two cases of contact anaphylaxis to milk proteins were reported in the literature (14, 15). They concerned infants aged 11 and 12

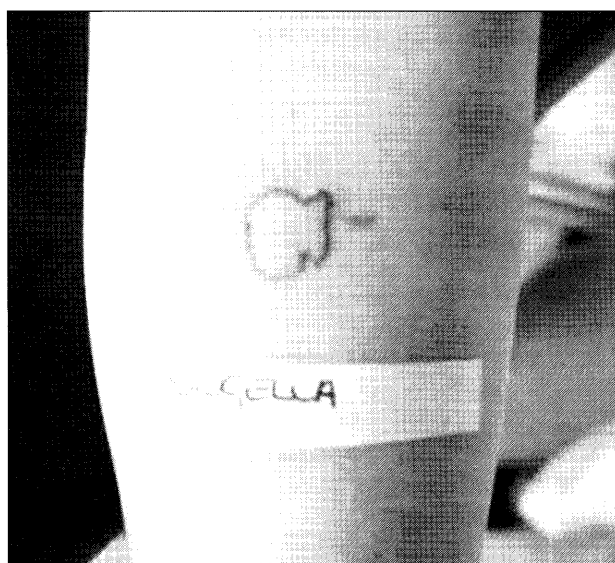


Fig. 2: Prick-test to Saugella® soap (case report 8).

months, who suffered anaphylaxis to milk from the early months of life. Within minutes of applying a skin healing cream for buttock erythema, the children suffered generalized urticaria, facial angioedema and asthma. These two reports illustrate the real risk of serious and systemic reaction to topical agents containing milk proteins in children allergic to milk. The two final cases in the literature refer to skin rash on AD in a context of known allergy to cow milk protein in two children aged 2 and 3 years, after using emollients containing milk proteins (16, 17).

If contact allergies to oats and milk concern principally children, contact allergies to sesame oil are seen mainly in adults, especially those with existing food allergy. We report the case of a 36-year old woman allergic to sesame presenting with facial angioedema and asthma after ingestion and who had contact urticaria within a few minutes of first using Yves Saint Laurent® Duo foundation cream (18) containing sesame oil. Prick-tests to sesame seed and to the foundation cream were positive (5 mm).

In the literature, the first cases of contact allergy to sesame oil reported in the 1970s were contact dermatitis (19) always in those using topical agents for ulcers on damaged and hyper-permeable skin. In 1975, Neering (20) reported as many as thirteen cases. The last case of contact dermatitis was published in 1986 (21) in an adult, ten days after application of a topical agent containing sesame oil for treatment of a burn on the forearm. Since then, only cases of contact urticaria have been published, two by Birnbaum et al. (22), two by Pecquet et al. (23), with cosmetics in patients known to be allergic to sesame. The risk of topical agents containing peanut is illustrated by a case of skin rash on AD in an infant allergic to cow milk protein after application of Bronchodermine®, a topical decongestant containing peanut oil. The role of peanut oil in cosmetics and pharmaceutical preparations causing skin sensitization was evidenced as early as 1991 (24) and later confirmed by Lack (25). Lack et al. (25) carried out a large cohort study in 13,000 pre-school children. Forty-nine were allergic to peanut and the diets of their mothers did not suggest any *in utero* sensitization since, in GB, pregnant women are put on strict nut eviction diets and specific IgE were not found in the cord blood. The authors considered the factors that might have explained the skin sensitization to peanut and found a significant relationship (RR 6.8) between peanut allergy and the earlier use of topical peanut-containing agents. One case of eczema was reported in the literature (26) in an infant with AD after skin care with soft almond oil. The patch-test was positive for soft almond oil, as was the prick-test and almond-specific IgE in this infant who had never ingested almond. Strid et al. (27) studied Balb/c mice bred and maintained

ned on a special diet free of peanut. The first group was exposed to peanut protein through barrier disrupted skin. On day 6, there was a mixed Th1/Th2 lymphocyte proliferation, on day 20 a clear Th2 predominance with an increase of specific IgE. In other groups of mice, primary exposure to peanut, via the percutaneous route, prevented the later development of tolerance, and in mice initially rendered tolerant to peanut, percutaneous exposure abolished it.

Finally, we report the case of an infant with AD and egg allergy. The AD persisted on the face despite an egg eviction diet. In fact, the mother used a shampoo containing egg proteins to wash the child's hair. When she stopped using the shampoo, all symptoms of AD resolved.

To summarize, traces of food proteins in topical skin agents and cosmetics may cause reactions in allergic people, infants more than adults, particularly infants with AD. These proteins seem to induce a sensitization that may lead to food allergy, as well as they can elicit immediate or delayed skin reactions in previously food allergic patients.

WHAT TO DO

Individuals: Given the hyper-permeability of infant skin, topical products containing food proteins of known allergenicity are contra-indicated for infants, and for patients with AD, which may be associated with skin hyper-permeability. Products for skin, containing oats or milk, or with any risk of contamination by wheat proteins (wheat starch for baths), have to be avoided in cases of AD for two reasons: firstly, the risk of percutaneous sensitization as has been demonstrated for peanut and suspected for oats, wheat and almond, and secondly, because of the risk of contact allergy, especially with wheat, nuts, milk and egg. In adults, the risk of contact allergy to food proteins in cosmetics mainly concerns those with history of food allergy (sesame, wheat), but we must bear in mind contact allergies to wheat hydrolysates, even in the absence of atopy and wheat sensitization.

A general rule: A clear and accurate identification of food allergens in cosmetics and topical agents is necessary, particularly with cosmetics where the same food protein has several INCI names. For

Age	Diagnosis	Incriminated product	Observed reaction	Positive skin tests
Two infants (case report 1)	AD	Skin-care product <i>Wheat starch</i> for baths	Immediate rash	Prick-test to wheat flour
Woman (case report 2)	Effort-induced anaphylaxis to wheat (secondary)	Cosmetic (shower gel) <i>Triticum vulgare</i>	Generalized erythema	Prick-test to wheat flour
Woman (case report 3)	Allergy to wheat flour	Cosmetic (shampoo) <i>Wheat proteins</i>	Contact eczema	Prick-test to wheat flour and shampoo
Woman (case report 4)	Allergy to wheat flour	Cosmetic (mascara) <i>Wheat proteins</i>	Facial angioedema and generalized urticaria	Prick-test to wheat flour and mascara
Infant (case report 5)	AD = CMA	Skin-care product (emollient cream) <i>Oats</i>	Exacerbated AD	Atopy patch-test to emollient cream
Infant (case report 7)	AD - CMA	Topical medicinal agent Gencifrice® (gum balm) <i>Lactis proteinum</i>	Contact urticaria	
Infant (case report 8)	AD- CMA	Skin-care product (Saugella® soap) <i>Micronized milk serum</i>	Generalized contact urticaria	Prick-tests to soap and cow milk
Woman (case report 9)	Food allergy to sesame	Skin-care product (foundation cream) <i>Sesame oil</i>	Contact urticaria	Prick-tests to foundation cream and sesame
Infant (case report 10)	AD	Topical medicinal decongestive (Bronchodremine®) <i>Peanut oil</i>	Rash on AD	Prick-tests to peanut
Infant (case report 11)	AD + allergy to egg	Cosmetic derivative (shampoo) <i>egg</i>	Persistent facial AD	Prick-test to egg

Table 1: Allergic reactions to food proteins in cosmetics and topical medicinal agents (Department of Internal Medicine, *Clinical Immunology and Allergology*).

AD: atopic dermatitis.

CMA: cow's milk allergy.

example, wheat proteins have several INCI names, identified on packaging as any of the following: gliadin, hydrolyzed wheat proteins, *triticum vulgare*. Furthermore, maternity departments should use food-protein-free skin care products for neonates. A telephone enquiry carried out in 22 maternity departments in Lorraine in 2003 showed that most used skin care products containing soft almond oil as well as wheat and milk proteins, in all healthy neonates....

CONCLUSION

Although allergic reactions to proteins in cosmetics and topical medicinal agents are rare, these products are commonly used and physicians should be aware of their allergenic potential, especially for atopic patients. Topical agents containing food proteins should not be prescribed in the event of atopy, especially in infants.

These reactions often occur after sensitization or previous food allergy. The hypothesis that they could induce a later food allergy has been validated for peanut-based products. The question is now posed for other proteins.

The legislation for pharmaceutical products and cosmetics should be adapted to take account of allergic diseases and all food allergens should be clearly printed on labels, as in the food industry.

References

1. Art L.511, L-658-10 (loi 75/604 du 10 juillet 1975) du Code de Santé Publique.
2. Directive européenne 76/768/CEE du 27 juillet 1976.
3. J.O.C.E n°L132 du 1er juin 1996 (décision 96/335/CE).
4. Directive européenne 2001/83/CE.
5. Collin P., Thorell L., Kaukinen K., Mäki M. - The safe threshold for gluten contamination in gluten-free products. Can trace amounts be accepted in the treatment of celiac disease? *Aliment Pharmacol Ther* 2004;19:1277-1283.
6. Kousa M., Strand R., Mäkinen-Kiljunen S., Hannuksela M. - Contact urticaria from hair conditioner. *Contact Dermatitis* 1990;23:279.
7. Niinimäki A., Niinimäki M., Mäkinen-Kiljunen S., Hannuksela M. - Contact urticaria from protein hydrolysates in hair conditioners. *Allergy* 1998;53:1078-1082.
8. Sanchez-Perez J., Sanz T., Garcia-Diez A. - Allergic contact dermatitis from hydrolyzed wheat protein in cosmetic cream. *Contact dermatitis* 2000;42:360.
9. Varjonen E., Petman L., Mäkinen-Kiljunen S. - Immediate contact allergy from hydrolyzed wheat cream in a cosmetic cream. *Allergy* 2000;55:294-6.
10. Pecquet C., Laurière M., Huet S., Leynadier F. - Is the application of a cosmetics-containing protein-derived products safe? *Contact Dermatitis* 2002;46:123.
11. Riboldi A., Pigatto P.-D., Altomare G.-F., Gibelli E. - Contact allergic dermatitis from oatmeal. *Contact Dermatitis* 1988;18:316-7.
12. Rancé F., Dargassies J., Dupuy P., Schmitt A.-M., Guérin L., Dutau G. - Faut-il contre-indiquer l'utilisation des émoullients à base d'avoine chez l'enfant atopique? *Rev Fr Allergol Immunol Clin* 2001 41:477-83.
13. de Paz Arranz S., Pérez Montero A., Zapatero Remon L., Martinez Molero M.-I. - Allergic contact urticaria to oatmeal. *Allergy* 2002;57:1215.
14. Lecks H.-I. - Anaphylaxis from milk protein in diaper ointment. *JAMA* 1980;244:1560.
15. Jarmoc L.-M., Primack W.-A. - Anaphylaxis to cutaneous exposure to milk protein in a diaper rash ointment. *Clin Pediatr* 1987;26:154-155.
16. Wang J. - Reactions of two young children with milk allergy after cutaneous exposure to milk-containing cosmetics products - *Arch Pediatr Adolesc Med* 2004;158:1089-90.
17. Milk-allergic children can have allergic reactions to cosmetic products. *Child Health Alert* 2004;22:3.
18. Dezfoulian B., De la Brassinne M. - Urticaire de contact par application d'un fond de teint contenant de l'huile de sésame. *Alim'inter* vol 7, n°6, nov 2002.
19. Van Dijk E., Dijk E., Neering H., Vitanyi B.-E. - Contact hypersensitivity to sesame oil in patients with leg ulcers and eczema. *Acta Derm Venereol.* 1973;53(2):133-5.
20. Neering H., Vitanyi B.-E., Malten K.-E., van Ketel W.-G., van Dijk E. - Allergens in sesame oil contact dermatitis. *Acta Derm Venereol.* 1975;55(1):31-4.
21. Kubo Y., Nonaka S., Yoshida H. - Contact sensitivity to unsaponifiable substances in sesame oil. *Contact Dermatitis.* 1986 Oct;15(4):215-7.
22. Birnbaum J., Porri F., Castelain M., Vervloet D. - Sesame seed and oil anaphylaxis. *J Allergy Clin Immunol* 1997;99:587.
23. Pecquet C., Leynadier F., Saiag P. - Immediate hypersensitivity to sesame in foods and cosmetics. *Contact Dermatitis* 1998 Dec; 39(6):313.
24. Moneret-Vautrin D.-A., Hatahet R., Kanny G., Ait-Djafer Z. - Allergenic peanut oil in milk formulas. *Lancet* 1991 Nov 2; 338(8775):1149.
25. Lack G., Northstone K., Golding J. - Avon longitudinal study of parents and children study team. Factors associated with the development of peanut allergy in childhood. *N Engl J Med.* 2003.13;348:977-85.
26. Guillet G., Guillet M.-H. - Sensibilisation alimentaire induite par l'huile d'amande douce chez le nourrisson: quel est le risque des topiques chez l'atopique? *La lettre du Gerda* 1998;16:14-16.
27. Strid J, Hourihane J., Kimbert I., Callard R., Strobel S. - Epicutaneous exposure to peanut protein prevents oral tolerance and enhances allergic sensitization. *Clin Exp Allergy* 2005;35:757-766.

