SENSITIZATION TO BENZYL SALICYLATE AND OTHER ALLERGENS IN PATIENTS WITH FRONTAL FIBROSING ALOPECIA

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ABSTRACT

Introduction: Contact sensitization is frequent among frontal fibrosing alopecia (FFA) patients (52-76%).

Objective: To evaluate the frequency of sensitization/photosensitization among an FFA population.

Material and methods: A population of FFA patients were patch tested (GEIDAC baseline; cosmetic and fragrance series), and photopatch tested (sunscreens series).

Results: 36 patients (mean age: 64.6 years old; 35/36: women) were studied. History of dermatitis was recorded in 69.4% (frequently involving the face). Overall, 80.5% patients showed positive patch test reactions. The most frequently positive allergens were nickel sulphate (25%); benzyl salicylate (22%); gallates (16.6%); propolis (16.6%); and limonene hydroperoxides (13.8%). Benzyl salicylate was likely relevant to the dermatitis (labelled on personal care products and most patients reporting clinical improvement with allergen avoidance). Patch tests with sunscreens showed positive reactions to 11 materials (5 patients). Photopatch tests were positive in one case.

Discussion: We speculate a possible relationship between sensitization to benzyl salicylate and FFA. Hypothetically, the most likely explanation is that sensitization to benzyl salicylate involving FFA patients is a consequence of increased exposure to it. It is unclear whether allergenic avoidance may impact the prognosis of alopecia. However, it seems to significantly improve the patients´ quality of life by lessening dermatitis and pruritus.

KEYWORDS: Benzyl Salicylate (CAS No 118-58-1); Frontal fibrosing alopecia; Allergic Contact Dermatitis; Patch tests; Photopatch tests; Gallates; propolis; scarring alopecia; sunscreen; fragrance.

1. INTRODUCTION

Frontal fibrosing alopecia (FFA) is an inflammatory type of alopecia where lichenoid lymphocytic infiltrates lead to perifollicular fibrosis and irreversible loss of follicles. It mainly concerns the frontal, preauricular areas as well as eyebrows, although other locations may also be involved. Since its first description in the early 90s, there has been a progressive increase in the incidence of this disorder, which currently represents a significant proportion of cases dermatologists routinely deal with across Spain, as well as in many other countries. Environmental factors have been hypothesized to impact this increasing occurrence.

In 2016, a retrospective study found that sunscreens were used by women with FFA twice as frequently as in controls[1]. The authors of these investigations also found frequent sensitization to contact allergens in this population. 52.5% had at least one positive patch test reaction, and linalool hydroperoxides and *Myroxylon pereirae* were significantly more common than in the overall patch-tested population[1]. After this research, other studies in different countries also found frequent contact sensitization among patients with FFA (up to 76%) (Table 1)[2-5]. In a recent article by Prasad, a surprisingly high frequency of sensitization to gallates as well as to other allergens was found[5].

OBJECTIVE

To evaluate the frequency of sensitization/photosensitization, the most frequent positive allergens and the frequency of clinical history of dermatitis among an FFA population.

2. MATERIAL AND METHODS

Patients who consulted with FFA from March 2019 to June 2019 in the Contact Dermatitis Units of two Dermatology Departments in Spain were offered the opportunity to be studied with extended patch test series including Spanish Contact Dermatitis Research Group (GEIDAC) series (TRUE Test® supplied by AllergEaze, SmartPractice, Calgary, Canada; supplementary allergens including propolis, hydroxyethyl methacrylate (HEMA) and some of the ESCD candidate allergens[6] (sodium metabisulfite, *Compositae* mix, linalool hydroperoxides 1%, limonene hydroperoxides 0.3%, benzisothiazolinone, octylisothiazolinone, decyl glucoside and lauryl polyglucoside, supplied by Chemotechnique, Vellinge, Sweden); cosmetics and fragrance series (Chemotechnique); as well as their personal care products. Photopatch tests were performed with some sunscreen compounds from the photoallergens series (2-hydroxy-4-methoxy-benzophenone; benzophenone-4; octocrylene; 3-(4-methylbenzylidene) camphor; 2-ethylhexyl-p-methoxycinnamate; isoamyl-p-methoxycinnamate; para-aminobenzoic acid; phenylbenzimidazolesulfonic acid; homosalate; methylene bis-benzotriazolyl tetramethylbutylphenol; bis-ethylhexyloxyphenol methoxyphenyl triazine; 2-(4-diethylamino-2-hydroxybenzoyl)-benzoic acid hexyl ester; octyl triazone; and disodium phenyl dibenzimidazole tetrasulfonate, AllergEaze) as well as their own sunscreen products. Exposure times and scoring readings were conducted according to the European Society of Contact Dermatitis (ESCD) guidelines[7]. Additionally, we included patients referred to us for investigation of eczema of any origin in whom exploration or clinical history revealed a concomitant FFA. Information regarding present or past history of dermatitis was also recorded, defined as the presence of lesions

diagnosed by us or described by the patients as very compatible. Intolerance to cosmetics or other items described by the patient as sole pruritus without lesions was not considered dermatitis. Epidemiological, clinical features (locations of the lesions; trichoscopic signs of current inflammatory activity, hair loss involving the eyebrows) were collected during the clinical examination. The daily, or almost daily, use of sunscreens, hair dye and hair lacquers as well as information as to whether the patients recalled distressing situations triggering the alopecia were registered.

3. RESULTS

36 patients with a mean age being 64.6 years old (39-86) were studied. All, except for one, were women. The pattern of alopecia was registered in 26/36 patients being linear in 14 (53.8%), diffuse (“zig-zag”) in 9 (34.6%), double band in 2 (7.69%), and androgenetic alopecia-like (AGA-like) in 1 (3.8%). Inflammatory activity was registered in 26 patients being clinically evident (perifollicular erythema, or hyperkeratosis) in 12 (46.1%); evident only on trichoscopy in 7 (27%) and absent in 7 (27%). Eyebrow alopecia was registered in 30 patients being partial, total and absent in 56.6%, 40% and 3.3% of the patients, respectively. Occipital involvement was actively assessed in 20 patients, being detected in 9 of them (45%). 17/30 (55.6%) of the patients declared to use sunscreens always or almost always; 10/30 (33.3%) used them only some months a year; and 3/30 (10%) rarely or never. 25/30 (83.3%) of the patients admitted to using hair dyes, and 20/30 (66.6%) used hair lacquers. 9/31 patients (29%) identified major stressors as triggers of their alopecia.

25/36 (69.4%) had a current or past history of dermatitis; 6/36 (16.6%) reported pruritus upon exposure to certain cosmetics without lesions; and 5/36 (13.8%) did not recall any symptoms or history of dermatitis. Dermatitis most frequently involved the face (in 13 patients), eyelids (6), neckline (4), hands (3), trunk (3), inframammary regions (2), scalp (1), lips (1), armpits (1), forearms (1), legs (1), thighs (1) and perianal area (1).

Patch tests with the GEIDAC baseline series and the patients´ personal items were performed in all cases.

Cosmetic series were performed on 31 patients (86.1%), 21 patients with dermatitis and 10 patients without dermatitis, showing positive results (at least one) in half of them (14 patients with dermatitis and 2 patients without dermatitis). Fragrance series were performed in 22 patients (61.1%), 15 patients with dermatitis and 7 patients without dermatitis, showing positive results (at least one) in 8 patients with dermatitis (and in none without dermatitis). Sunscreen compounds (from the photo-allergen series) were performed in 25 patients.

11 patients developed positive patch test reactions to their own products and materials (including 13 diverse items such as cosmetics and sun blockers as well as one minoxidil solution and one patient´s work uniform fabric pieces).

Overall, 29/36 patients (80.5%) showed positive patch test reactions: 22/25 patients with dermatitis (88%) and 7/11 patients without dermatitis (63.6%).

The most frequent positive allergens were nickel sulphate in 9 patients (25%); benzyl salicylate (8; 22%); gallates (6; 16.6%) (octyl gallate in 5, dodecyl gallate in 1 and propyl gallate in 1); propolis (6; 16.6%); and limonene hydroperoxides (5; 13.8%).

Other positive allergens are shown on Table 1.

The intensity of the reactions to benzyl salicylate were: 2+ (1); 1+ (4); and ?+ (3). The weaker reactions involved 2 patients showing ?+ reactions to benzyl salicylate on both cosmetic and fragrance series sites (which allowed us to verify the reactions by “double-checking”) and one additional patient reacting to both benzyl salicylate and phenyl salicylate.

One benzyl salicylate-sensitized patient developed systemic symptoms following patch tests on D2 (following the removal of the patches). The patient reported malaise, headache, nausea and progressive diffuse facial erythema and pruritus. One additional patient stated that the patch test reaction to benzyl salicylate (which was clearly positive on D2) persisted for around two weeks.

5/6 patients sensitized to propolis also showed positive results to benzyl salicylate; 4/5 of the patients sensitized to octyl gallate were also sensitized to propolis (and 3 of them additionally to benzyl salicylate) (Fig. 1). All patients sensitized to gallates, benzyl salicylate and/or propolis had a current or past history of dermatitis (Fig. 2) except for one patient who reacted to benzyl salicylate and did not show any lesions or recall any previous signs of dermatitis. 3/8 patients sensitized to benzyl salicylate reacted to other salicylates (1 to homosalate; 1 to phenyl salicylate; and 1 to homosalate and ethylhexyl salicylate).

Benzyl salicylate was determined to be possibly relevant in most cases. It was identified on the labels of a wide variety of personal care products of all the patients sensitized to it, including sunscreens, shampoos, hair lacquers, fine fragrances, deodorants, moisturizers and hand lotions. Additionally, four patients sensitized to benzyl salicylate who recently came to our office for

follow-up, reported significant clinical improvement of dermatitis and quality of life enhancement (through a lessening of the pruritus) with benzyl salicylate avoidance. However, some of these patients were sensitized to other allergens, thus definite relevance could not be proved. Propolis could only be identified in a shampoo belonging to a patient sensitized to propolis, benzyl salicylate and octyl gallate.

Patch tests with sunscreens showed positive reactions without photoaggravation to 11 materials involving 5 patients: octocrylene, benzophenone-3 and the sunscreen Heliocare mineral® (IFC, Spain) containing butyloctyl salicylate (in one patient who was also sensitized to benzyl salicylate and octyl gallate) (Fig. 2); homosalate, ethylhexyl salicylate and butyl methoxydibenzoylmethane (in one patient sensitized to benzyl salicylate and propolis); homosalate (in one patient sensitized to benzyl salicylate and octyl gallate); butyl methoxydibenzoylmethane (in one patient with a positive reaction to her own filter which contained it); and another patient with positive patch tests to two of her own sunscreens (both containing ethylhexyl salicylate which was not patch tested). Photopatch tests were all negative except for only one patient who developed a reaction to benzophenone-4 only on irradiated skin. This reaction could not be reproduced over time.

4. DISCUSSION

We hereby report the results of a series of patients with FFA patch/photopatch tested with extended series and their own personal care products. A current or past history of dermatitis elsewhere as well as positive patch tests were observed in a high proportion of patients (69.4% and 80.5%, respectively). In

addition, we unexpectedly observed that benzyl salicylate was the most frequently positive allergen (22%) after nickel sulphate. To the best of our knowledge, sensitization to it has not been described thus far in this context. Gallates, previously described to be frequent among FFA patients[5], were also frequently positive in our series.

Benzyl salicylate (CAS No 118-58-1), an ester of benzyl alcohol and salicylic acid, is a cosmetic ingredient with perfuming and UV absorbing functions. When used as a fragrance, its presence should be indicated in the list of ingredients when its concentration exceeds 0.001 % in leave-on products and 0.01% in rinse-off products. The International Fragrance Association (IFRA) Standard limits range from 0.5% benzyl salicylate in lip products to 12.8% in oral care products[8].

It has been considered to be an uncommon allergen. The last update of the GEIDAC registry (REIDAC) in June 2020 showed a frequency of sensitization to it of 1.1% among the general patch tested population. This registry shows data of the patch tested population across Spain reported by the members of the GEIDAC (to which our hospitals have contributed to with the results of our patients, including the cases reported in this study during the same period). Regarding patch tests performed in consecutive patients, Silvestre et al., in a retrospective multicenter Spanish study (2011-2015), found that 23/1013 (2.2%) patients patch tested with the fragrance series were positive to benzyl salicylate[9]. Similarly, Sheman et al. systematically patch tested it in 600 individuals in the USA (2014-2016), finding a frequency of sensitization to it of 2.2%[10]. Additionally, benzyl salicylate 2% pet. resulted in no photoallergic reactions in patients with contact dermatitis in different studies[8].

Clinically, sensitization to benzyl salicylate has been typically described in relation to two scenarios: eyelid allergic contact dermatitis from hair products[11,12] and pigmented allergic contact dermatitis[13,14]. Also, long-term daily application of hair sunscreen spray with benzyl salicylate to the hair part line of the scalp has been published to likely perpetuate the lesions of lichen planopilaris in a woman[15].

Regarding sources of exposure of benzyl salicylate, according to one market study performed by us in 2018 regarding fragrances in consumer goods (unpublished results), it was labelled in 61% of female fine fragrances; 26% of 699 cosmetics and hygiene products sold in the supermarket; 9% of 135 cosmetics sold in herbs stores; 8% of 88 cosmetics sold in the pharmacies; and 8% of 306 domestic cleaning products. None of the 188 topical medications were labelled to contain it (although 2 contained *Myroxylon pereirae*). Among the products sold in supermarkets, benzyl salicylate was labelled in 46% and 33% of the “leave-on” and “rinse-off” hair products, respectively; 34% of the deodorants; and 18% of the sunscreens. A recent study showed that 60% and 51% of leave-on and rinse-off hair care products contained sunscreen or UV-absorbing compounds, being benzyl salicylate, benzophenone-4 and ethylhexyl methoxycinnamate the most frequently found[16].

According to our previous research, benzyl salicylate was less frequently labelled in domestic cleaning products than other fragrances. The cleaners where benzyl salicylate was most frequently labelled were multipurpose cleaners. This finding is in agreement with the study published by Wieck et al.[17].

There seems to be an association between the exposure to benzyl salicylate and FFA, arguments in favour of this hypothesis being: 1. benzyl salicylate (as

well as other salicylates) are frequent components of shampoos, sunscreens, and other cosmetics; 2. a more frequent use of said products among women with FFA has been reported[1, 18-21]; 3. according to our findings, both a history suggestive of dermatitis and sensitization to benzyl salicylate may be frequent among patients with FFA; 4. this sensitization seems likely to be clinically relevant to the dermatitis in most patients (present in the patients´ personal care products and allergenic avoidance leading to a significant clinical dermatitis improvement); 5. benzyl salicylate is able to penetrate the human epidermis as well as naked rat and guinea pig skins at considerable concentrations in different skin penetration and in vitro absorption studies[8]; 6. benzyl salicylate has been described to have estrogenic activity and be able to cause hormonal disruption[8, 22-24]; 7. salicylates have been described to moderate the activities of some enzymes (such as aromatase or follicular sulfotransferase)[25]; 8. there seem to be overlapping clinicopathological features between pigmented contact dermatitis (historically linked to benzyl salicylate) and lichen planus pigmentosus (described in relation to FFA)[26,27].

The most likely explanation for this hypothetical association is that sensitization to benzyl salicylate in patients with FFA is a consequence of an increased exposure to it in cosmetics more frequently used by these patients or in other unknown sources. As an example, the patients would hypothetically abuse hair lacquers containing it in an attempt to cover the bald areas. An increased exposure would then imply a higher risk for sensitization. Once the allergic contact dermatitis develops, it could contribute to the activity of FFA through *koebnerization* (Fig. 3).

Conversely, a hypothetical involvement of benzyl salicylate in the etiopathogenesis of the FFA could be considered. The alopecia would happen as a result of the sensitization itself (as a particular type of non-eczematous lichenoid contact dermatitis with tropism for the follicles) or through other conjectural mechanisms. A possibility is that benzyl salicylate (and/or another compound) is able to both cause sensitization and eventually trigger contact dermatitis and, at the same time, cause or worsen FFA through an independent pathway such as, for example, hormonal disruption, enzymatic modulation or other (Fig. 3).

Systemic exposure to benzyl salicylate involved in sensitization and/or dermatitis elicitation cannot be ruled out since salicylates are present in food as well as oral medications and could also possibly be inhaled from hair sprays, face powders and other airborne formulations[8]. Natural dietary sources of salicylates are alcoholic beverages, herbs and spices (such as mint containing 54.2 mg kg^{-1}; cumin: 29.7 mg kg^{-1}; thyme: 28.6 mg kg^{-1}paprika: 28.2 mg kg^{-1}), fruits, vegetables, etc.[28]. Additionally, salicylates are added to processed food as flavourings[8]. Daily salicylic acid intake varies markedly, ranging from 0.4 to 200 mg day[28].

Interestingly, in our population, in addition to benzyl salicylate, several other allergens that are also used in food as additives and flavourings were frequently found positive (gallates, sorbitan derivatives, sodium metabisulfite or limonene). Inversely, allergens frequently found in cosmetics (including hair cosmetics), such as methylisothiazolinone, paraphenylenediamine or other fragrances were rare or absent from our series. Additionally, one of our patients developed a

systemic reaction from patch tests proving that the allergen can be absorbed and trigger systemic symptoms.

Other possible sources are absorbent hygiene products. Benzyl salicylate at concentrations higher than 30 µg/g has been detected in both the top sheets as the absorbent layer of one panty liner[29].

Benzyl salicylate is a component of propolis, which may explain why all patients reacting to propolis were also positive to benzyl salicylate[30]. The high proportion of positive propolis among our patients could be due to the fact that the population attending our hospitals live in rural areas holding a large number of colonies of honeybee hives. However, in that case, we would expect benzyl salicylate to be less frequent than propolis and show less intense reactions, and in our patients, it was the reverse. In the same way, benzyl salicylate may cross react with *Myroxylon pereirae*, which could explain the positive reactions to it in some of our patients as well as in previously published series[1-5].

The association of benzyl salicylate and octyl gallate is less clear. One possible explanation is the exposure to both in a common source (cosmetics, food or other). However, in our experience, we have not found caprylyl gallate (INCI name of octyl gallate) in any cosmetic product brought in by any of the patients, and octyl gallate was banned as a food additive in the EU in 2019[31]. Dodecyl gallate and octyl gallate (caprylyl gallate) are used in cosmetics as antioxidants and should be labelled as such, but propyl gallate can also be used for its fragrance properties. We hypothesize with the possibility that some manufactures may elude its specific labelling this way.

An alternative explanation for the association of benzyl salicylate and octyl gallate is a hypothetical cross-reactivity on account of their chemical structure

similarities (benzyl salicylate -benzyl 2-hydroxybenzoate- and octyl gallate -octyl 3,4,5-trihydroxybenzoate). This premise would need further investigation. Interestingly, Prasad et al. found that gallates represented 25% of the positive reactions of patch tests in a group of FFA (mainly propyl gallate, which, in our series, only involved one single patient who was also allergic to octyl gallate). Prasad´s patients were patch tested with cosmetic series, but no cases of sensitization to benzyl salicylate were observed (manufacturer is not mentioned in the article, but leading manufacturers include it in their cosmetic series). Gallates (especially propyl gallate) have been linked to cheilitis from lipsticks involving female patients[32]. However, only one of our patients showed involvement of the lips (a patient with positive dodecyl gallate only).

The weaker reactions to benzyl salicylate in some of our patients could be due to the volatile nature of the allergen. Double-checking the positive reactions in both cosmetic and fragrance series seems a sensible method to confirm these results. Said reactions could as well be irritant, although benzyl salicylate appears to have low irritant potential when patch tested according to published research[8].

Benzyl salicylate is a fragrance of mandatory declaration when the concentration exceeds certain limits, making it easier to avoid. However, benzyl salicylate naturally occurs in some essential oils such as ylang-ylang oil, carnation oil and tuberose absolute[8]. Some products containing these essential oils could contain benzyl salicylate without specifying its presence on the label.

To summarize, we found an unexpectedly high frequency of current or past dermatitis of any kind and topographical distribution as a concomitant event or co-morbidity in a series of FFA patients, as well as sensitization, particularly to

benzyl salicylate, gallates, and propolis. Photopatch tests were negative in most cases. More studies are needed to verify whether these findings apply to other populations with FFA.

We hypothesize with the possibility of a relationship between sensitization to benzyl salicylate and FFA. However, it is uncertain whether there is a relationship of causation. Likely, benzyl salicylate or any of the other positive allergens are responsible for the lesions of dermatitis but not for the FFA. In our opinion, FFA patients may frequently use certain types of cosmetics and often become sensitized to their components. The possible impact of this sensitization on FFA pathogenesis is a mere hypothesis (Fig. 3).

In our patients, the frequency of sensitization to benzyl salicylate is 22% (30% among the patients with a history of dermatitis) which is much higher than the 1% observed in the general patch tested population in our region during the same period, and also higher than the 2% of patch tests performed in consecutive patients in other studies. That observation is, in our opinion, a notable unexpected finding. However, this is a case series and the lack of statistical analysis comparing our results with a control group is a significant limitation. Our research signifies a preliminary approach and hopefully will boost further more extensive studies.

According to our findings, it seems practical to patch test patients with FFA, preferentially those with a history of dermatitis. Adding benzyl salicylate, gallate and propolis to the baseline series seem helpful in this setting. We recommend preparing the patch tests immediately before their application to avoid loss through evaporation and carefully look for weak reactions that may be meaningful. It is also useful to perform patch tests and photopatch tests with the

patient´s own sunscreen products. It is unclear whether allergenic avoidance may lead to an arrest in the progression of alopecia. However, it seems to significantly improve the symptoms of concomitant dermatitis and the patients´ quality of life through the lessening of pruritus. Until more evidence is gathered, we propose our patients with FFA use cosmetic products free of salicylates and fragrances. We also recommend that they use mineral sunscreens without fragrances or salicylates.

REFERENCES

1. Aldoori N, Dobson K, Holden CR, McDonagh AJ, Harries M, Messenger AG. Frontal fibrosing alopecia: possible association with leave-on facial skin care products and sunscreens; a questionnaire study. *Br J Dermatol*. 2016;175(4):762-7.
2. Rocha VB, Donati A, Contin LA, et al. Photopatch and patch testing in 63 patients with frontal fibrosing alopecia: a case series. *Br J Dermatol*. 2018;179(6):1402-1403.
3. Aerts O, Bracke A, Goossens A, Meuleman V, Lambert J. Titanium dioxide nanoparticles and frontal fibrosing alopecia: cause or consequence? *J Eur Acad Dermatol Venereol*. 2019;33(1): e45-e46.
4. Rudnicka L, Rokni GR, Lotti T, et al. Allergic contact dermatitis in patients with frontal fibrosing alopecia: An international multi-center study. *Dermatol Ther*. 2020; 12: e13560.
5. Prasad S, Marks DH, Burns LJ, et al. Patch testing and contact allergen avoidance in patients with lichen planopilaris and/or frontal fibrosing alopecia: A cohort study. *J Am Acad Dermatol*. 2020;83(2):659-661.
6. Wilkinson M, Gonçalo M, Aerts O, et al. The European baseline series and recommended additions: 2019. *Contact Dermatitis*. 2019;80(1):1-4.
7. Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. *Contact Dermatitis.* 2015;73(4):195–221.

8. Safety assessment of benzyl salicylate as used in cosmetics. https://www.cir-safety.org/sites/default/files/Benzyl%20Salicylate.pdf Accessed November 2, 2020.
9. Silvestre JF, Mercader P, González-Pérez R, et al. Sensitization to fragrances in Spain: A 5-year multicentre study (2011-2015). *Contact Dermatitis*. 2019;80(2):94-100.
10. Scheman A, Te R. Contact Allergy to Salicylates and Cross-Reactions. *Dermatitis*. 2017;28(4):291.
11. Fernández-Canga P, Ruíz-González I, Varas-Meis E, Valladares-Narganes LM, Rodríguez-Prieto MA. Contact allergy to benzyl salicylate. *Contact Dermatitis*. 2017;76(5):315-316.
12. Tous-Romero F, Prieto-Barrios M, Andrés-Lencina JJ, de Frutos JO. Allergic contact dermatitis caused by benzyl salicylate in hair products. *Contact Dermatitis*. 2018;79(5):310-311.
13. Zaaroura H, Bergman R, Nevet MJ. Pigmented Facial Contact Dermatitis to Benzyl Salicylate: A Comparative Histopathological and Immunohistochemical Study of the Involved Skin and the Positive Patch Test Site. *Am J Dermatopathol*. 2019;41(6):443-447.
14. Alagappan U, Tay YK, Lim SP. Pigmented contact dermatitis secondary to benzyl salicylate. *Acta Derm Venereol*. 2013;93(5):590.
15. Canavan TN, McClees SF, Duncan JR, Elewski BE. Lichen Planopilaris in the Setting of Hair Sunscreen Spray. *Skin Appendage Disord*. 2019;5(2):108-110.

16. Callander J, Frost J, Stone N. Ultraviolet filters in hair-care products: a possible link with frontal fibrosing alopecia and lichen planopilaris. *Clin Exp Dermatol*. 2018;43(1):69-70.
17. Wieck S, Olsson O, Kümmerer K, Klaschka U. Fragrance allergens in household detergents. *Regul Toxicol Pharmacol*. 2018;97:163-169.
18. Debroy Kidambi A, Dobson K, Holmes S, et al. Frontal fibrosing alopecia in men: an association with facial moisturizers and sunscreens. *Br J Dermatol*. 2017;177(1):260-261.
19. Cranwell WC, Sinclair R. Sunscreen and facial skincare products in frontal fibrosing alopecia: a case-control study. *Br J Dermatol*. 2019 Apr;180(4):943-944.
20. Cranwell WC, Sinclair R. Frontal fibrosing alopecia: Regrowth following cessation of sunscreen on the forehead. *Australas J Dermatol*. 2019;60(1):60-61.
21. Moreno-Arrones OM, Saceda-Corralo D, Rodrigues-Barata AR, et al. Risk factors associated with frontal fibrosing alopecia: a multicentre case-control study. *Clin Exp Dermatol.* 2019;44(4):404-410.
22. Charles AK, Darbre PD. Oestrogenic activity of benzyl salicylate, benzyl benzoate and butylphenylmethylpropional (Lilial) in MCF7 human breast cancer cells in vitro. *J Appl Toxicol*. 2009;29(5):422-34.
23. Kunz PY, Fent K. Multiple hormonal activities of UV filters and comparison of in vivo and in vitro estrogenic activity of ethyl-4-aminobenzoate in fish. *Aquat Toxicol*. 2006;79(4):305-24.
24. Jiménez-Díaz I, Molina-Molina JM, Zafra-Gómez A, et al. Simultaneous determination of the UV-filters benzyl salicylate, phenyl salicylate, octyl

salicylate, homosalate, 3-(4-methylbenzylidene) camphor and 3-benzylidene camphor in human placental tissue by LC-MS/MS. Assessment of their in vitro endocrine activity. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2013; 936:80-7

25. Suchonwanit P, Thammarucha S, Leerunyakul K. Minoxidil and its use in hair disorders: a review. *Drug Des Devel Ther.* 2019; 13:2777-2786.
26. Berliner JG, McCalmont TH, Price VH, Berger TG. Frontal fibrosing alopecia and lichen planus pigmentosus. *J Am Acad Dermatol*. 2014;71(1): e26-7.
27. Romiti R, Biancardi Gavioli CF, Anzai A, Munck A, Costa Fechine CO, Valente NYS. Clinical and Histopathological Findings of Frontal Fibrosing Alopecia-Associated Lichen Planus Pigmentosus. *Skin Appendage Disord*. 2017;3(2):59-63.
28. Duthie GG, Wood AD. Natural salicylates: foods, functions and disease prevention. *Food Funct*. 2011;2(9):515-20.
29. Desmedt B, Marcelis Q, Zhilivoda D, Deconinck E. Sensitizing fragrances in absorbent hygiene products. *Contact Dermatitis*. 2020;82(5):279-282.
30. Hausen BM, Wollenweber E. Propolis allergy. (III). Sensitization studies with minor constituents. *Contact Dermatitis*. 1988;19(4):296-303.
31. COMMISSION REGULATION (EU) 2018/1481 of 4 October 2018 amending Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council and the Annex to Commission Regulation (EU) No 231/2012 as regards octyl gallate (E 311) and dodecyl gallate (E 312). https://eur-lex.europa.eu/legal-

content/EN/TXT/PDF/?uri=CELEX:32018R1481&from=ES. Accessed November 2, 2020.

32. García-Melgares ML, de la Cuadra J, Martín B, Laguna C, Martínez L, Alegre V. Sensibilización por galatos. Revisión de 46 casos [Sensitization to gallates: review of 46 cases]. *Actas Dermosifiliogr*. 2007;98(10):688-93.

FIGURES

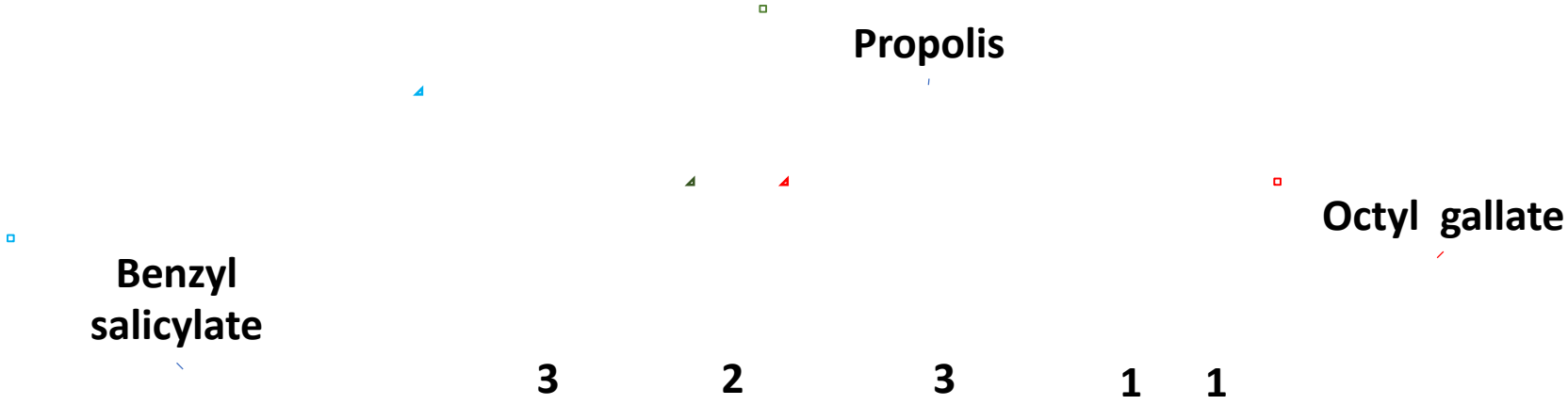
Figure 1. Association between benzyl salicylate, propolis and octyl gallate. Sensitization to benzyl salicylate, propolis and octyl gallate simultaneously involved several patients.

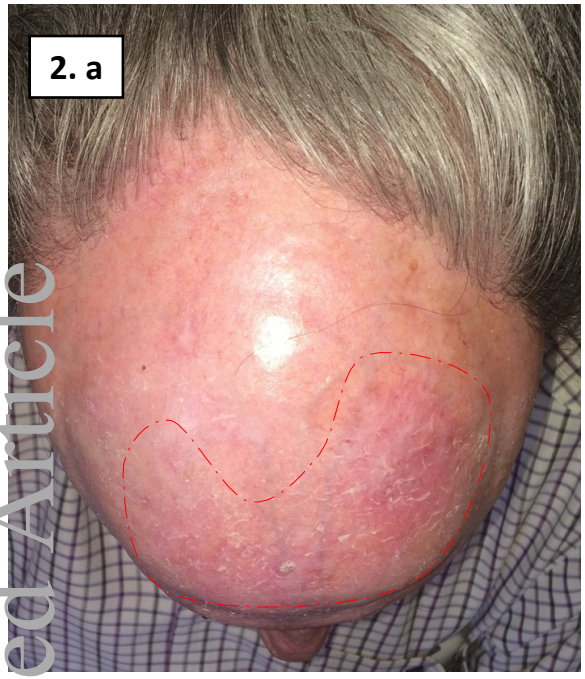
Figure 2. An 86-year-old man diagnosed with long-lasting frontal fibrosing alopecia (FFA). **2. A.** The patient presented with daily episodes of dermatitis involving his forehead and temples lasting years. Lesions were highly itchy. **2. B.** Total hair loss bilaterally involving the eyebrows. **2. C.** Advanced stage of FFA involving the forehead and retroauricular areas. Patchy eczematous changes. **2.D.** FFA with occipital involvement. **2.E.** Dermoscopic features suggestive of cicatricial alopecia with loss of follicular units, absence of vellus hair and slight interfollicular erythema. **2. F.** The patient was sensitized to benzyl salicylate, octyl gallate and propolis as well as decyl glucoside, benzyl benzoate, *Evernia furfuracea, Evernia prunasti*, and many sunscreen compounds (octocrylene, benzophenone-3 and his own sunscreen Heliocare mineral, IFC, Torrejón de Ardoz, Spain). Benzyl salicylate was present in both the hair lacquer and fine fragrance the patient had been using daily for years. The positive sunscreen Heliocare contained butyl octyl salicylate. Additionally, he used another sunscreen with ethyl hexyl salicylate (which could not be patch tested). The dermatitis cleared and his quality of life significantly improved with the avoidance of positive allergens.

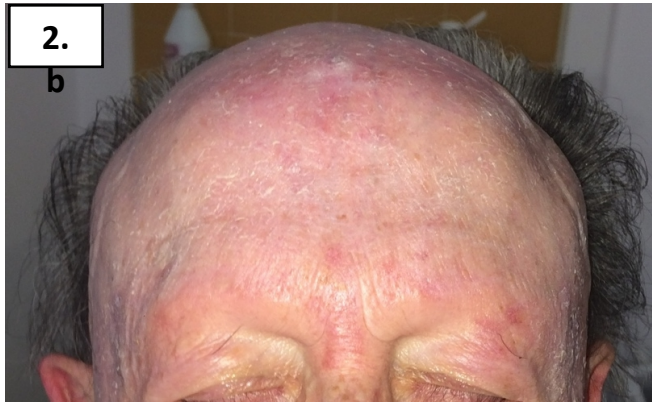
Figure 3. Alternative hypothesis of an association between frontal fibrosing alopecia (FFA) and sensitization to benzyl salicylate (or other allergens). **4. A.** The frontal fibrosing alopecia (FFA) would trigger an increased exposure to

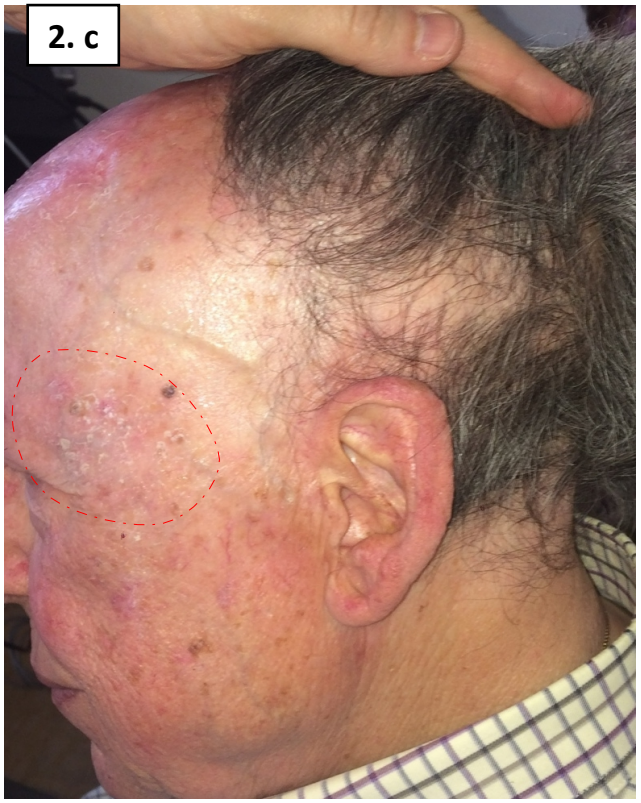
sources with benzyl salicylate (or other allergens) leading to sensitization and elicitation of contact dermatitis. Contact dermatitis could secondarily aggravate the FFA condition through a *Koebner* phenomenon.

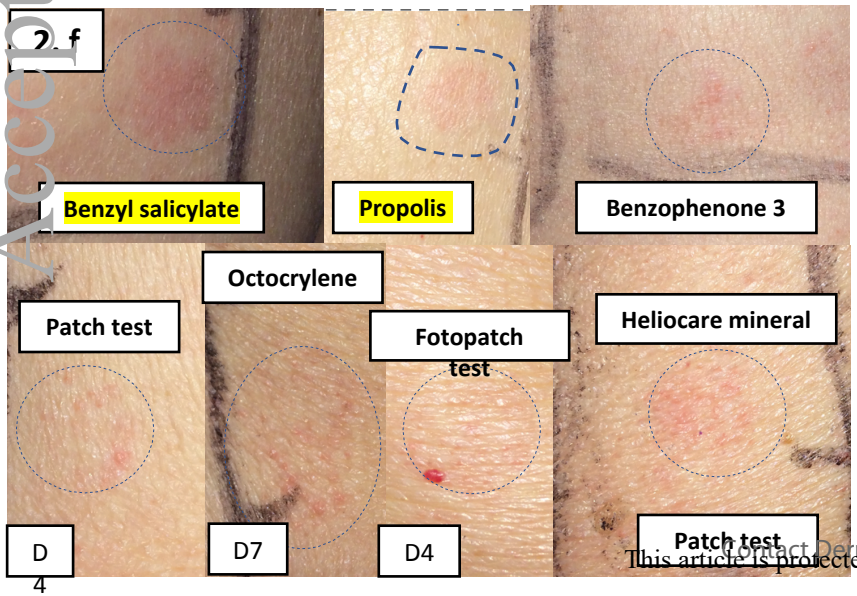
4. B: Hypothetically, the alopecia could happen as a result of the sensitization (FFA being itself a type of non-eczematous type of reaction). **4. C**: Alternatively, one or several compounds would cause both sensitization and eventual contact dermatitis and, at the same time, cause or worsen FFA through an independent pathway.

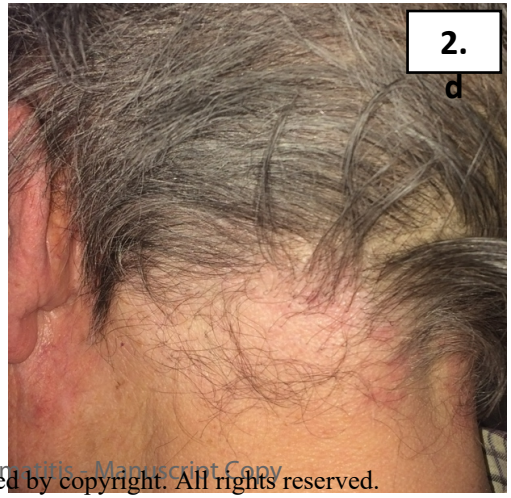


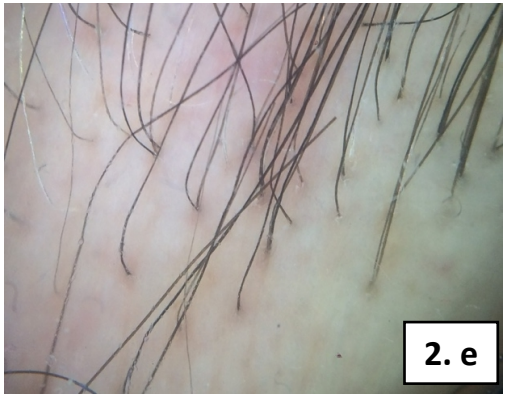


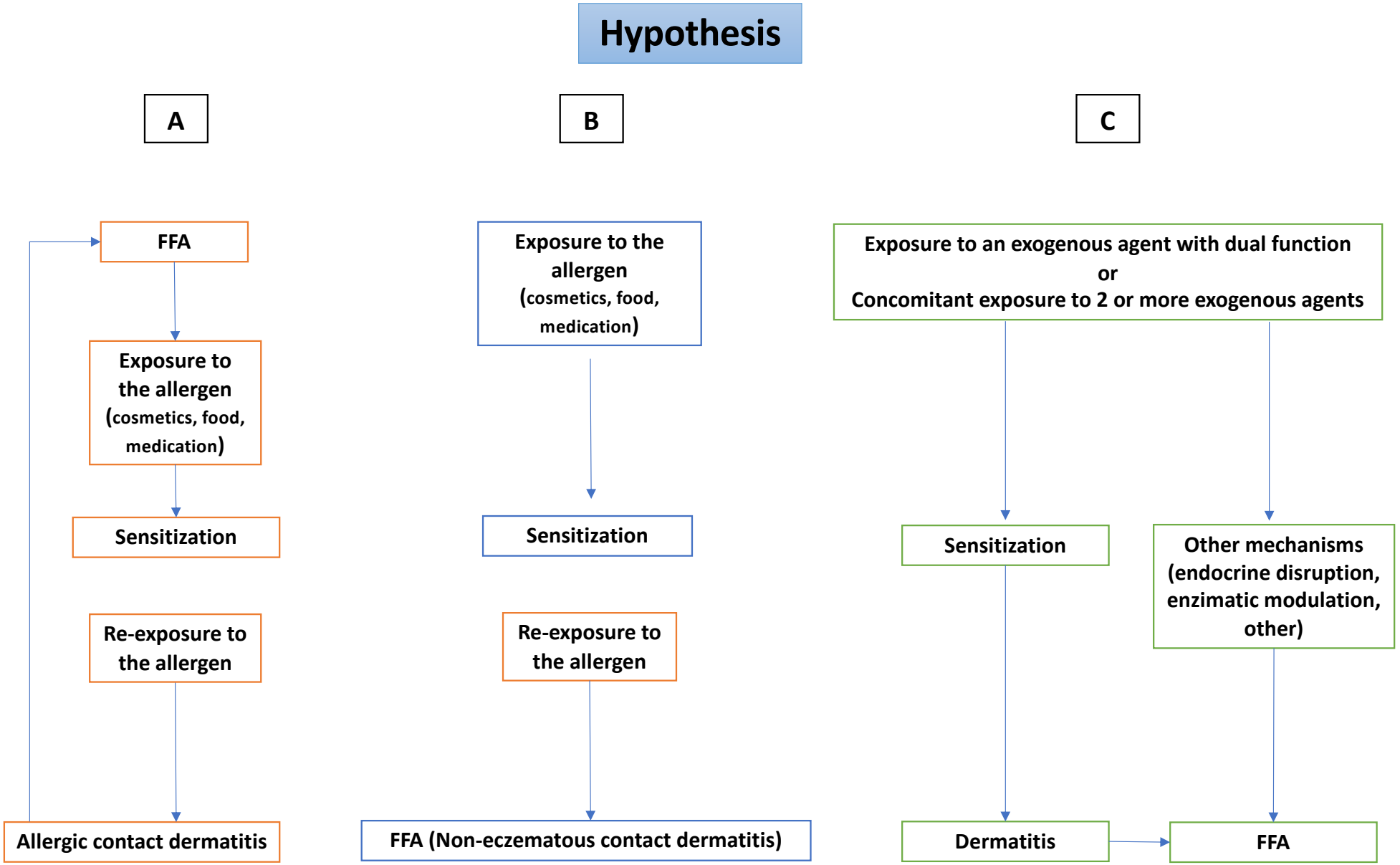











Hypothesis
A
B
C
FFA
Exposure to the allergen (cosmetics, food, medication)
Sensitization
Re-exposure to the allergen
Allergic contact dermatitis
Exposure to the allergen (cosmetics, food, medication)
Sensitization
Re-exposure to the allergen
FFA (Non-eczematous contact dermatitis)
Exposure to an exogenous agent with dual function
or
Concomitant exposure to 2 or more exogenous agents
Sensitization
Other mechanisms (endocrine disruption, enzimatic modulation, other)
Dermatitis
FFA

TABLES

Table 1. Studies exploring the frequency of contact sensitization through patch testing among populations of frontal fibrosing alopecia (FFA).

	Year		n	Patch tests series	Photopatch tests series	% Frequency of positive tests	More frequent allergens
Aldoori[1]	2016	UK	40	British baseline series, LimOH, LinOH		52.5%	LinOH and *Myroxylon pereirae* (significantly more frequently positive than in overall patch tested population)
Rocha[2]	2018	Brazil	Patch tests (63) and photopatch tests (41)	European Photopatch Baseline Series; Brazilian baseline series; cosmetic series; methylisothiazolinone; LimOH, LinOH; FM II.	European photopatch baseline series; nickel; *Myroxylon pereirae*; MI; potassium dichromate; FM I and II; PPDA; chlorhexidine; triclosan; MCI–MI.	59% (relevant positive results in 27%)	Nickel (19%); fragrances (8%): photoallergy to chromium (1)

Aerts[3]	2019	Belgium	8 FFA	titanium dioxide 10% pet., titanium (III) nitride 5% pet., titanium (IV) oxalate hydrate 5% pet., titanium 10% pet., calcium titanate 10% pet. (Chemotechnique®, Vellinge, Sweden); TiO2 NP 25% in cremor cetomacrogolis		All negative	
Rudnicka[4]	2020	Multi-national	20 FFA (24 controls)	Baseline series		65% (37% in controls p=0,003)	Cobalt (II) chloride hexahydrate (35%); nickel (II) sulfate hexahydrate (25%); potassium dichromate (15%); In controls: cobalt (II) chloride hexahydrate (33.3%); potassium dichromate (20.8%); nickel (II) sulfate hexahydrate (16.6%)
Prasad[5]	2020	USA	42 cases of FFA and/or LPP (2018-2019)	North American Baseline Series; cosmetic series; hairdresser series; N-isopropyl-N9-phenyl- p-phenylenediamine; MCI/MI; benzophenone-4; avobenzone; benzalkonium chloride;		76%	Gallates (26%); dodecyl gallate (16.7%), octyl gallate (4.8%), propyl gallate (4.8%), linalool (19%); FM I (14%); FM II (9.5%); benzophenone-4 (14.3%); ammonium persulfate (14.3%);

				carvone; polysilicon 15; aminoazobenzene			propolis (9.5%); benzoyl peroxide (9.5%); *Myroxylon pereirae* (7%); MI/MCI (11.9%)
Pastor-Nieto	2020	Spain	36 cases of FFA	GEIDAC series (36) and some of the ESCD candidate allergens: SMB, *Compositae* mix, BIT, OIT, decyl glucoside, lauryl polyglucoside, linOH, limOH, propolis, HEMA); cosmetic (31); sunscreens from photoallergen series (25); fragrances (22).	Sunscreen series and patient´s own sunscreens	80.5%	nickel sulphate (25%); benzyl salicylate (22%); gallates (16.6%); propolis (16.6%); and LimOH (13.8%); cobalt chloride (3); thiomersal (3); SMB (3); sorbitan derivatives (3); decyl glucoside (3); FMI (3, one of them being sensitized to cinnammyl alcohol; and another one to *Evernia prunasti* and *Evernia furfuracea*); potassium dichromate (2); LinOH (2); *Myroxylon pereirae* (2); HEMA (2, of which one was also sensitized to HPMA, EGDMA, and TEGDMA); MDBGN (2); jasmine absolute (1); EDA (1); neomycin (1); chlorhexidine (1); MI plus BIT (1); and textile dye

							mix plus disperse blue 106 and disperse orange 1(1).

Abbreviations: BIT: benzisothiazolinone; EDA: ethylenediamine; EGDMA: ethyleneglycol dimethacrylate; FFA: frontal fibrosing alopecia; FM: fragrance mix; HEMA: hydroxyethyl methacrylate; HPMA: hydroxypropyl methacrylate, LimOH: limonene hydroperoxides; LinOH: linalool hydroperoxides; LPP: lichen planopilaris; MCI/MI: methylchloroisothiazolinone/methylisothiazolinone; MDBGN: methyldibromo glutaronitrile; MI: methylisothiazolinone; OIT: octyl isothiazolinone; PPDA: para-phenylenediamine; SMB: sodium metabisulfite; TiO2 NP: titanium dioxide nanoparticles; TEGDMA: triethyleneglycol dimethacrylate.