Tangled Truths: Unraveling the Link Between Frontal Fibrosing Alopecia and Allergic Contact Dermatitis

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PRACTICE **POINTS**

- Frontal fibrosing alopecia (FFA), a variant of lichen planopilaris (LPP), is an increasingly prevalent type of scarring alopecia that may have a closer relationship to contact allergy than was previously understood. However, there is no evidence of a causal association to date.
- When evaluating for FFA/LPP, clinicians should assess for use of cosmetic products or sunscreens that may have a potential impact on the disease course.

Frontal fibrosing alopecia (FFA) is an increasingly common diagnosis, especially in middle-aged women, and has garnered growing attention in the scientific literature. This variant of lichen planopilaris (LPP) is recognized as a progressive scarring alopecia affecting the frontal and temporal regions of the scalp as well as the eyebrows and occasionally other sites. Although its precise etiology remains elusive, various factors such as genetics, medications, hormonal influences, and environmental exposures—including specific chemicals present in sunscreens—have been implicated in its pathogenesis but without evidence of causality. The potential relationship between contact allergy and FFA has been explored, with some suggesting an increased prevalence of contact allergy among patients diagnosed with FFA. This article aims to explore the potential association between contact allergy and FFA, focusing on the current published literature and implicated allergens.

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Frontal fibrosing alopecia (FFA) is an increasingly common diagnosis, especially in middle-aged women, and was first described by Kossard[1] in 1994. It is a variant of lichen planopilaris (LPP), a progressive scarring cicatricial alopecia that affects the frontotemporal area of the scalp, eyebrows, and sometimes even body hair.[1] Although its etiology remains unclear, genetic causes, drugs, hormones, and environmental exposures—including certain chemicals found in sunscreens—have been implicated in its pathogenesis.[2,3] An association between contact allergy to ingredients in personal care products and FFA diagnosis has been suggested; however, there is no evidence of causality to date. In this article, we highlight the potential relationship between contact allergy and FFA as well as clinical considerations for management.

Clinical Features and Diagnosis

Frontal fibrosing alopecia typically manifests with gradual symmetric recession of the frontal hairline leading to bandlike hair loss along the forehead, sometimes extending to the temporal region.[4] Some patients may experience symptoms of scalp itching, burning, or tenderness that may precede or accompany the hair loss. Perifollicular erythema may be visible during the early stages and can be visualized on trichoscopy. The affected skin may appear pale and shiny and may have a smooth texture with a distinct lack of follicular openings. Aside from scalp involvement, other manifestations may include lichen planus pigmentosus, facial papules, body hair involvement, hypochromic lesions, diffuse redness on the face and neck, and prominent frontal veins.[5] Although most FFA cases have characteristic clinical features and trichoscopic findings, biopsy for histopathologic examination is still recommended to confirm the diagnosis and ensure appropriate treatment.[4] Classic histopathologic features

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include perifollicular lymphocytic inflammation, follicular destruction, and scarring.

Pathophysiology of FFA

The pathogenesis of FFA is thought to involve a variety of triggers, including immune-mediated inflammation, stress, genetics, hormones, and possibly environmental factors.[6] Frontal fibrosing alopecia demonstrates considerable upregulation in cytotoxic helper T cells (T_H1) and IFN-γ activity resulting in epithelial hair follicle stem cell apoptosis and replacement of normal epithelial tissue with fibrous tissue.[7] There is some suspicion of genetic susceptibility in the onset of FFA as suggested by familial reports and genome-wide association studies.[8-10] Hormonal and autoimmune factors also have been linked to FFA, including an increased risk for thyroid disease and the postmenopausal rise of androgen levels.[6]

Allergic Contact Dermatitis and FFA

Although they are 2 distinct conditions with differing etiologies, allergic contact dermatitis (ACD) and FFA may share environmental triggers, especially in susceptible individuals. This may support the coexistence and potential association between ACD and FFA.

In one case report, a woman who developed facial eczema followed by FFA showed positive patch tests to the UV filters drometrizole trisiloxane and ethylhexyl salicylate, which were listed as ingredients in her sunscreens. Avoidance of these allergens reportedly led to notable improvement of the symptoms.[11] Case-control studies have found an association between the use of facial sunscreen and risk for FFA.[12] A 2016 questionnaire that assessed a wide range of lifestyle, social, and medical factors related to FFA found that the use of sunscreens was significantly higher in patients with FFA than controls ($P<.001$), pointing to sunscreens as a potential contributing factor, but further research has been inconclusive. A higher frequency of positive patch tests to hydroperoxides of linalool and balsam of Peru (BoP) in patients with FFA have been documented; however, a direct cause cannot be established.[2]

In a 2020 prospective study conducted at multiple international centers, 65% (13/20) of FFA patients and 37.5% (9/24) of the control group had a positive patch test reaction to one or more allergens ($P=.003$). The most common allergens that were identified included cobalt chloride (positive in 35% [7/20] of patients with FFA), nickel sulfate (25% [5/20]), and potassium dichromate (15% [3/20]).[13] In a recent 2-year cohort study of 42 patients with FFA who were referred for patch testing, the most common allergens included gallates, hydroperoxides of linalool, and other fragrances.[14] After a 3-month period of allergen avoidance, 70% (29/42) of patients had decreased scalp erythema on examination, indicating that avoiding relevant allergens may reduce local inflammation. Furthermore, 76.2% (32/42) of patients with FFA showed delayed-type hypersensitivity to allergens found in daily personal care products such as shampoos, sunscreens, and moisturizers, among others.[14] Notably, the study lacked a control group. A case-control study of 36 Hispanic women conducted in Mexico also resulted in 83.3% (15/18) of patients with FFA and 55.5% (10/18) of controls having at least 1 positive patch test; in the FFA group, these included iodopropynyl butylcarbamate (16.7% [3/18]) and propolis (16.7% [3/18]).[15]

Most recently, a retrospective study conducted by Shtaynberger et al[16] included 12 patients with LPP or FFA diagnosed via clinical findings or biopsy. It also included an age- and temporally matched control group tested with identical allergens. Among the 12 patients who had FFA/LPP, all had at least 1 allergen identified on patch testing. The most common allergens identified were propolis (positive in 50% [6/12] of patients with FFA/LPP), fragrance mix I (16%), and methylisothiazolinone (16% [2/12]). Follow-up data were available for 9 of these patients, of whom 6 (66.7%) experienced symptom improvement after 6 months of allergen avoidance. Four (44.4%) patients experienced decreased follicular redness or scaling, 2 (22.2%) patients experienced improved scalp pain/itch, 2 (22.2%) patients had stable/improved hair density, and 1 (1.1%) patient had decreased hair shedding. Although this suggests an environmental trigger for FFA/LPP, the authors stated that changes in patient treatment plans could have contributed to their improvement. The study also was limited by its small size and its overall generalizability.[16]

These studies have underscored the significance of patch testing in individuals diagnosed with FFA and have identified common allergens prevalent in this patient population. They have suggested that patients with FFA are more likely to have positive patch tests, and in some cases patients could experience improvements in scalp pruritus and erythema with allergen avoidance; however, we emphasize that a causal association between contact allergy and FFA remains unproven to date.

Most Common Allergens Pertinent to FFA

Preservatives—In some studies, patients with FFA have had positive patch tests to preservatives such as gallates and methylchloroisothiazolinone/methylisothiazolinone (MCI/MI).[14] Gallates are antioxidants that are used in food preservation, pharmaceuticals, and cosmetics due to their ability to inhibit oxidation and rancidity of fats and oils.[17] The most common gallates include propyl gallate, octyl gallate, and dodecyl gallate. Propyl gallate is utilized in some waxy or oily cosmetics and personal care items including sunscreens, shampoos, conditioners, bar soaps, facial cleansers, and moisturizers.[18] Typically, if patients have a positive patch test to one gallate, they should be advised to avoid all gallate compounds, as they can cross-react.

Similarly, MCI/MI can prevent product degradation through their antibacterial and antifungal properties. This combination of MCI and MI is used as an effective method of prolonging the shelf life of cosmetic products and commonly is found in sunscreens, facial moisturizing creams,

shampoos, and conditioners[19]; it is banned from use in leave-on products in the European Union and Canada due to increased rates of contact allergy.[20] In patients with FFA who commonly use facial sunscreen, preservatives can be a potential allergen exposure to consider.

Iodopropynyl butylcarbamate also is a preservative used in cosmetic formulations. Similar to MCI/MI, it is a potent fungicide and bactericide. This allergen can be found in hair care products, bodywashes, and other personal products.[21]

UV Light–Absorbing Agents—A systematic review and meta-analysis conducted in 2022 showed a significant ($P<.001$) association between sunscreen use and FFA.[22] A majority of allergens identified on patch testing included UVA- and UVB-absorbing agents found in sunscreens and other products including cosmetics,[11,12] such as drometrizole trisiloxane, ethylhexyl salicylate, avobenzone, and benzophenone-4. Drometrizole trisiloxane is a photostabilizer and a broad-spectrum UV filter that is not approved for use in sunscreens in the United States.[23] It also is effective in stabilizing and preventing the degradation of avobenzone, a commonly used UVA filter.[24]

Fragrances—Fragrances are present in nearly every personal and cosmetic product, sometimes even in those advertised as being "fragrance free." Hydroperoxides of linalool, BoP, and fragrance mix are common allergens that are found in a variety of personal care products including perfumes, cosmetics, and even household cleaning supplies.[25] Simultaneous positive patch tests to BoP and fragrance mix are common due to shared components. Linalool can be found in various plants such as lavender, rose, bergamot, and jasmine.[26] Upon air exposure, linalool auto-oxidizes to form allergenic hydroperoxides of linalool. Among patients with FFA, positive patch test reactions to fragrance chemicals are common and could be attributed to the use of fragranced hair products and facial cosmetics.

Hair Dyes and Bleaches—Allergic reactions to hair dyes and bleaches can result in severe ACD of the head/neck and, in rare cases, scarring alopecia.[27] Chemicals found in these products include paraphenylenediamine (PPD) and ammonium persulfate. The most common hair dye allergen, PPD also is used in some rubbers and plastics. Ammonium persulfate is a chemical used in hair bleaches and to deodorize oils. One case study reported a patient with FFA who developed chemically induced vitiligo immediately after the use of a hair color product that contained PPD.[28] However, without patch testing to confirm the presence of contact allergy, other patient-specific and environmental risk factors could have contributed to FFA in this case.

A Knot in the Truth

In this endeavor to untangle the truth, it should be remembered that at the time of writing, the purported association between FFA and ACD remains debatable. Contact dermatitis specialists have voiced that the association between FFA and ACD, especially with regard to sunscreen, cannot be supported due to the lack of sufficient evidence.[29] A large majority of the research conducted on FFA and ACD is based on case reports and studies limited to a small sample size, and most of these patch test studies lack a control group. Felmingham et al[30] noted that the recent epidemiology of FFA aligns with increased sunscreen use. They also highlighted the limitations of the aforementioned studies, which include misclassification of exposures in the control group[2] and recall bias in questionnaire participants.[2,12] The most pressing limitation that permeates through most of these studies is the temporal ambiguity associated with sunscreen use. A study by Dhana et al[31] failed to specify whether increased sunscreen use preceded the diagnosis of FFA or if it stems from the need to protect more exposed skin as a consequence of disease. Broad sunscreen avoidance due to concern for a possible association with hair loss could have detrimental health implications by increasing the risk for photodamage and skin cancer.

FFA Patch Testing

The avoidance of pertinent allergens could be effective in reducing local inflammation, pruritus, and erythema in FFA.[9,14,32] At our institution, we selectively patch test patients with FFA when there is a suspected contact allergy. Clinical features that may allude to a potential contact allergy include an erythematous or eczematous dermatitis or symptoms of pruritus along the scalp or eyebrows. If patients recall hair loss or symptoms after using a hair or facial product, then a potential contact allergy to these products could be considered. Patch testing in patients with FFA includes the North American 80 Comprehensive Series and the cosmetic and hairdresser supplemental series, as well as an additional customized panel of 8 allergens as determined by patch testing experts at the University of Massachusetts, Brigham and Women's Hospital, and Massachusetts General Hospital (private email communication, November 2017). Patch test readings are performed at 48 and 96 or 120 hours. Using the

Most Common Allergens in Frontal Fibrosing Alopecia

Balsam of Peru[2,33]
Benzophenone-4[33]
Fragrances[14,16]
Gallates[14]
Hydroperoxides of linalool[2,14,33]
Iodopropynyl butylcarbamate[15]
Metals (eg, nickel sulfate, cobalt chloride)[11]
Methyldibromoglutaronitrile[15]
Methylisothiazolinone[14]
Propolis[15,16]

American Contact Dermatitis Society's Contact Allergen Management Program, patients are provided personalized safe product lists and avoidance strategies are discussed.

Final Interpretation

In a world where cosmetic products are ubiquitous, it is hard to define the potential role of contact allergens in the entangled pathogenesis of FFA and ACD. As evidenced by emerging literature that correlates the 2 conditions and their exacerbating factors, it is important for physicians to have a comprehensive diagnostic approach and heightened awareness for potential allergens at play in FFA (Table). The identification of certain chemicals and preservatives as potential triggers for FFA should emphasize the importance of patch testing in these patients; however, whether the positive reactions are relevant to the pathogenesis or disease course of FFA still is unknown. While these findings begin to unravel the intertwined causes of FFA and ACD, further research encompassing larger cohorts and prospective studies is imperative to solidify these associations, define concrete guidelines, and improve patient outcomes.

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