Risk factors for frontal fibrosing alopecia: A case-control study in a multiracial population

Paulo Müller Ramos, MD, PhD,[a] Alessandra Anzai, MD,[b] Bruna Duque-Estrada, MD,[c] Debora Cadore Farias, MD,[d] Daniel Fernandes Melo, MD, MSc,[e] Fabiane Mulinari-Brenner, MD, MSc,[f] Giselle Martins Pinto, MD,[g] Leonardo Spagnol Abraham, MD, MSc,[h] Leopoldo Duailibe Nogueira Santos, MD,[i] Rodrigo Pirmez, MD,[c] and Hélio Amante Miot, MD, PhD[a]

Botucatu, São Paulo, Rio de Janeiro, Florianópolis, Curitiba, Porto Alegre and Brasília, Brazil

Background: Frontal fibrosing alopecia (FFA) is a chronic cicatricial alopecia with unknown etiology and a worldwide rising incidence.

Objective: The objective of this study was to evaluate the association of FFA with demographic and exposure factors in a Brazilian multiracial population.

Methods: A multicenter case-control study was conducted in 11 referral centers throughout Brazil. The study was a case-control study that prospectively recruited 902 participants (451 patients with FFA and 451 sex-matched control individuals). Study participants completed a thorough questionnaire comprising variables grouped as baseline demographics, environmental exposure, diet, hormonal factors, allergies, and hair and skin care.

Results: When adjusted by sex, age, menopause, and skin color, FFA was associated with hair straightening with formalin (odds ratio [OR], 3.18), use of ordinary (nondermatologic) facial soap (OR, 2.09) and facial moisturizer (OR, 1.99), thyroid disorders (OR, 1.69), and rosacea (OR, 2.08). Smokers (OR, 0.33) and users of antiresidue/clarifying shampoo (OR, 0.35) presented a negative association with FFA. There was no association with the use of sunscreen.

Limitations: Recall bias.

Conclusions: The association with moisturizers, ordinary facial soap, and hair straightening with formalin and the negative association with antiresidue/clarifying shampoo reinforce the possibility of an exogenous particle triggering FFA. (J Am Acad Dermatol 2021;84:712-8.)

Key words: case-control; frontal fibrosing alopecia; risk factors; sunscreens; tobacco.

Frontal fibrosing alopecia (FFA) is a primary scarring lymphocytic alopecia of unknown etiology initially described in 1994.[1] It has been considered a variant of lichen planopilaris, presenting with similar histopathologic findings.[2,3] This condition affects mainly postmenopausal women and leads to progressive frontotemporal hairline recession, frequently associated with eyebrow hair loss.[4,5] The clinical spectrum of FFA has been expanded to include generalized body hair

From the Universidade Estadual Paulista, Botucatu[a]; Universidade de São Paulo[b]; Santa Casa de Misericórdia do Rio de Janeiro[c]; Universidade Federal de Santa Catarina, Florianópolis[d]; Universidade Estadual do Rio de Janeiro[e]; Universidade Federal do Paraná, Curitiba[f]; Santa Casa Misericórdia, Porto Alegre[g]; Universidade de Brasília, Brasília[h]; and Santa Casa de São Paulo, São Paulo.[i]

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Correspondence to: Paulo Müller Ramos, MD, PhD, Av; Prof. Mário Rubens Guimarães Montenegro, sn, São Paulo State University—UNESP, Campus Botucatu, 18618687, Botucatu, São Paulo, Brazil. E-mail: dermato.paulo@gmail.com.

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loss and skin involvement, such as facial papules and lichen planus pigmentosus.[6,7]

There is no precise epidemiologic data of its population prevalence, but recently, FFA was classified as an emerging epidemic because of the clear perception of worldwide rising incidence in the last decade.[8,9] Currently, there is no curative treatment for FFA, and patients experience permanent hair loss.[10,11]

The etiopathogenesis of FFA is still unknown. Genetic predisposition was recently reinforced by its association with some human leukocyte antigen (HLA) class I alleles.[12,13] Considering the increasing incidence, one current hypothesis is that environmental triggers may act over a genetic predisposition, driving the T helper (Th) type 1/JAK-STAT profile of inflammation in FFA.[14,15]

Recently, 4 case-control studies in white populations linked FFA with the use of sunscreens.[16-19] However, a causal correlation is still highly controversial.[20-22] No case-control study has evaluated FFA in Asian, black, or even a highly miscegenated population (eg, Brazilian population).

Here, we aimed to evaluate and describe the association of FFA with the use of sunscreens and other possible external factors in a Brazilian sample.

CAPSULE SUMMARY

- The relation of frontal fibrosing alopecia (FFA) with environmental factors is still controversial.
- According to this study, FFA was associated with moisturizers, ordinary (nondermatologic) facial soap, and formalin hair straightening. Use of antiresidue/clarifying shampoo and smoking were suggested as protective factors. FFA was not associated with sunscreens.

METHODS

Participants

We conducted a multicenter case-control study for which we prospectively recruited 902 participants (451 patients with FFA and 451 sex-matched control individuals) from March 2018 to December 2019 in 11 centers throughout Brazil. Inclusion criteria for cases were age older than 18 years and a confirmed diagnosis of FFA by a dermatologist. Control individuals were patients from the same centers with the diagnosis of nonscarring alopecia, confirmed by a dermatologist.

Study participants completed a thorough electronic questionnaire comprising variables grouped as baseline demographics, environmental exposure, diet, hormonal factors, allergies, and hair and skin care. The questions referred to exposures that occurred 5 years before the onset of alopecia for cases and before study inclusion for the control individuals.

The study protocol was approved by the institutional review board of Universidade Estadual Paulista and conducted in accordance with the principles of the Declaration of Helsinki.

Sample size and statistical analysis

Sample size was estimated to detect up to 10% differences in the proportions among case patients and control individuals (α = 0.01; power, 0.80).[23]

Qualitative variables are presented as percentages, and quantitative variables are presented as mean and standard deviation if normality was concluded by the Shapiro-Wilk test.[24]

The age of perceived FFA onset was evaluated according to the main clinical and demographic variables through a general linear model. The effect size was expressed by the β coefficient of regression.

The variables were grouped in 3 blocks for the exploratory analysis: personal characteristics, exposure, and cleansing/hairstyle. The associations of variables were assessed by using a conditional multiple logistic regression model adjusted by age, sex, and skin color. The final model was composed of those that reached P of 0.1 or less (corrected by the Benjamini-Hochberg procedure) within the primary analysis.[25,26] Posteriorly, the analysis of the sensitivity of the results was performed, stratifying the sample according to skin color or age group.[27]

The effect size was expressed as the odds ratio (OR) and its 95% confidence interval (CI). Statistical significance was set as P of .001 or less (2-tailed analysis).[28]

RESULTS

A total of 451 patients with FFA and 451 sex-matched control individuals were enrolled. Regarding baseline data, age and skin color were slightly different between the 2 groups. The female predominance (96%; 95% CI, 94-98), high familial occurrence (9%; 95% CI, 6-12), and age at disease onset near menopause (47 years; 95% CI, 46-48) were remarkable (Table I). The most common nonscarring alopecia diagnoses among control individuals were female pattern alopecia (58%), telogen effluvium (25%), and alopecia areata (13%).

In this sample, FFA was associated with hair straightening with formalin (OR, 3.18), the regular

Abbreviations used:

CI: confidence interval
FFA: frontal fibrosing alopecia
HLA: human leukocyte antigen
IL: interleukin
OR: odds ratio
Th: T helper

use of ordinary (nondermatologic) facial soap (OR, 2.09), and facial moisturizing creams (OR, 1.99). Moreover, 76% of patients with FFA experienced an intense stressful event just before the onset of the disease. Smokers (OR, 0.33) and regular users of antiresidue/clarifying shampoo (OR, 0.35) presented a negative association with FFA (Tables II and III).

The sensitivity analysis of the results from Table III was performed through the stratification of the sample according to skin color and age group (Supplemental Tables I-IV; available via Mendeley at https://doi.org/10.17632/yczrgmjwb8.1), and the overall results kept their consistency in the subgroup analysis.

Regarding the age of perceived FFA onset, participants with first-degree familial occurrence presented the disease earlier (β = −5.69; P = .007). Nevertheless, age at FFA onset was not associated with female sex (β = 2.90; P = .342) or darker skin color (β = 2.84; P = .539).

The main reported comorbidities by patients with FFA and control individuals are presented in Table IV. Thyroid disorders (OR, 1.69) and rosacea (OR, 2.08) were more prevalent among patients with FFA.

Table I. Baseline data from participants

Characteristics	Patients with FFA	Control individuals	*P* value
n	451	451	
Age, y, mean (SD)	53 (13)	49 (14)	.001
Sex, n (%)			
Female	434 (96)	434 (96)	>.999
Male	17 (4)	17 (4)	
BMI, kg/m^2, mean (SD)	26 (5)	25 (5)	.759
Skin color, n (%)			
White	132 (29)	146 (32)	.004
Fair	179 (40)	212 (47)	
Brown	112 (25)	78 (17)	
Black	28 (6)	15 (3)	
Education, n (%)			
Elementary	49 (11)	53 (12)	.557
High school	82 (18)	62 (14)	
College	320 (71)	336 (75)	
Age at FFA onset, y, mean (SD)	47 (12)	NA	
First degree familial with FFA, n (%)	41 (9)	NA	

BMI, Body mass index; *FFA,* frontal fibrosing alopecia; *NA,* not applicable; *SD,* standard devation.

DISCUSSION

Despite strong evidence of a genetic background, the increasing worldwide incidence suggests a role of some environmental exposure in FFA development.[4,12] In this study, FFA was associated with long-term use of facial moisturizers, ordinary (nondermatologic) soap for facial washing, and hair straightening with formalin, but it was not associated with regular use of sunscreens. Smoking and use of antiresidue/clarifying shampoo were suggested as protective factors.

The main theory to explain the association of sunscreens and leave-on skin care products with FFA is that exogenous particles could penetrate the follicular infundibulum and elicit a lichenoid inflammatory reaction. The association with topical products was observed in 4 previous case-control studies.[16-19] Our results support the association with facial moisturizers but not with sunscreens. Additionally, there was an association with the use of ordinary facial soap compared to soaps prescribed by dermatologists.

General questionnaire-based surveys are unable to determine specific ingredients from each facial skin care product that could be related to FFA, because most participants report only the brands and not their specific composition. Regardless of the specific substance, the protective effect of antiresidue/clarifying shampoo could be explained by the more efficient removal of exogenous particles that could penetrate the follicular infundibulum and trigger inflammation in patients within a genetically predisposing background.[29]

Unlike this study, all 4 previous case-control questionnaires observed higher recall rates of sunscreen use among patients with FFA: Aldoori et al[16] evaluated 105 women with FFA and 100 age- and sex-matched control individuals (48% vs 24%); Debroy et al[17] evaluated 17 men with FFA and 73 age- and sex-matched control individuals (35% vs 4%); Moreno-Arrones et al[18] evaluated 289 women with FFA and 289 sex-matched control individuals (48.1% vs 34.9%) and 19 men with FFA and 58 sex-matched control individuals (31.6% vs 6.9%)[1]; and Cranwell and Sinclair[19] evaluated 130 women with FFA and 130 age- and sex-matched control individuals (92% vs 40%). Nevertheless, the more frequent use of moisturizers in FFA reached statistical significance only when men were evaluated. Despite racial differences, variations in country regulations

Table II. Comparison of patients with FFA and control individuals (with nonscarring alopecia) according to the main variables of the study

Variables	Patients with FFA	Control individuals	OR (CI 95%)*	*P* value*
Personal characteristics				
BMI, kg/m^2, mean (SD)	25.6 (4.7)	25.1 (4.5)	1.00 (0.97-1.03)	.940
Education, n (%)				.059
College	320 (71)	336 (75)	2.11 (1.23-3.61)	
High school	82 (18)	62 (14)	1.75 (1.10-2.78)	
Elementary	49 (11)	53 (12)	1.00 (—)	
Live with a partner, n (%)	308 (68)	317 (70)	0.98 (0.73-1.31)	.909
Number of children, mean (SD)	1.6 (1.3)	1.4 (1.5)	0.99 (0.89-1.11)	.884
Menopause, n (%)	272 (60)	200 (44)	1.49 (0.98-2.28)	.137
Exposure, n (%)				
Live in rural area, n (%)	27 (6)	30 (7)	0.70 (0.40-1.23)	.368
Live near an agricultural field, n (%)	37 (8)	62 (14)	0.49 (0.31-0.76)	.001
Live near heavy industry, n (%)	56 (12)	46 (10)	1.20 (0.78-1.84)	.544
Live near cell phone antenna, n (%)	93 (21)	88 (20)	1.11 (0.80-1.55)	.643
Live near high-tension lines, n (%)	73 (16)	65 (14)	1.21 (0.84-1.76)	.496
Passive smoking, n (%)	85 (19)	62 (14)	1.37 (0.95-1.97)	.172
Current smoking, n (%)	46 (10)	87 (19)	0.42 (0.29-0.63)	.001
Regular alcohol intake, n (%)	206 (46)	210 (47)	1.09 (0.83-1.43)	.639
Vegetarian, n (%)	9 (2)	11 (2)	0.72 (0.29-1.80)	.614
Artificial sweeteners, n (%)	165 (37)	194 (43)	0.78 (0.60-1.03)	.160
Work in front of a computer, n (%)	264 (59)	253 (56)	1.47 (1.10-1.97)	.030
Sun exposure, minutes/day, mean (SD)	43.0 (64.3)	31.1 (37.1)	1.00 (1.00-1.01)	.051
Sunscreen use, n (%)				.100
Regularly >5 years ago	180 (40)	159 (35)	1.15 (0.84-1.56)	
Regularly <5 years ago	84 (19)	116 (26)	0.72 (0.51-1.03)	
Never/occasionally	187 (42)	176 (39)	1.00 (—)	
Facial moisturizing, n (%)				.016
Regularly >5 years ago	199 (44)	146 (32)	1.70 (1.24-2.33)	
Regularly <5 years ago	103 (23)	112 (25)	1.21 (0.85-1.72)	
Never/occasionally	149 (33)	193 (43)	1.00 (—)	
Cleansing/hairstyling				
Antiresidue shampoo	15 (3)	49 (11)	0.29 (0.16-0.54)	.008
Nondermatologic facial soap	322 (71)	240 (53)	1.90 (1.43-2.54)	.001
Hair dying	249 (55)	209 (46)	1.16 (0.86-1.57)	.509
Hair straightening (nonformalin)	79 (18)	68 (15)	1.17 (0.81-1.69)	.566
Hair straightening (formalin)	116 (26)	51 (11)	2.99 (2.06-4.34)	.002

BMI, Body mass index; *CI,* confidence interval; *FFA,* frontal fibrosing alopecia; *OR,* odds ratio; *SD,* standard deviation.
*Adjusted by sex, age, and skin color (corrected by Benjamini-Hochberg procedure).

of substances and preservatives present in sunscreens and moisturizers may explain these discrepancies.[30]

FFA was associated with hair straightening with formalin. Many straighteners contain phenolic products, which can mediate inflammatory response, DNA methylation, and carcinogenesis, even under chronic low-level exposure.[31-33] FFA was also previously associated with work exposure to alkylphenols,[18] suggesting a possible role of formaldehyde releasers in the etiopathogenesis of FFA.

Formaldehyde releasers are widely used as preservatives in cleansers, cosmetics, moisturizers, sunscreen, and hair care products. The most common substances are quaternium-15, dimethylol dimethyl hydantoin, imidazolidinyl urea, diazolidinyl urea, polyoxymethylene urea, sodium hydroxymethylglycinate, bronopol, and glyoxal. They are also well-known allergens, and they are subjected to different regulations (maximum concentrations) worldwide.[34] There is an increasing trend in contact dermatitis due to fragrances and preservatives, especially isothiazolinones, formaldehyde, and formaldehyde releasers, which is related to industrialization.[35-38] The increased use of preservatives and fragrances in cleansing and leave-on products may be associated with the increase in FFA incidence.[39-41]

Table III. Final multivariate model for the comparison among patients with FFA and control individuals (nonscarring alopecia)

Variables	Odds ratio (CI 95%)*	*P* value*
Education		.188
College	1.44 (0.83-2.52)	
High school	1.74 (0.96-3.15)	
Elementary	1 (—)	
Live near an agricultural field	0.49 (0.30-0.78)	.003
Current smoking	0.33 (0.21-0.51)	<.001
Work in front of a computer	1.48 (1.04-2.10)	.031
Sun exposure, minutes/day	1.01 (1.00-1.01)	.008
Sunscreen use		.296
Regularly >5 years ago	1.06 (0.74-1.52)	
Regularly <5 years ago	0.78 (0.52-1.16)	
Never/occasionally	1 (—)	
Facial moisturizing		.001
Regularly >5 years ago	1.99 (1.39-2.86)	
Regularly <5 years ago	1.49 (1.01-2.20)	
Never/occasionally	1 (—)	
Antiresidue shampoo	0.35 (0.19-0.67)	.001
Nondermatologic facial soap	2.09 (1.50-2.90)	<.001
Hair straightening (formalin)	3.18 (2.11-4.80)	<.001

CI, Confidence interval; *FFA,* frontal fibrosing alopecia.
*Adjusted by sex, menopause, age, and skin color. *P* (model) <.001; *P* (constant) = .002; *P* (Hosmer and Lemeshow) = .459. Power, 99%; R^2 (Nagelkerke) = 0.235; correct classification, 68.1%.

Table IV. Frequency of the main reported comorbidities among patients with FFA and control individuals

Comorbidities	Patients with FFA, n (%)	Control individuals, n (%)	*P* value
Rhinitis	132 (29)	147 (33)	.280
Gastritis/reflux	106 (24)	92 (20)	.260
Sinusitis	116 (26)	120 (27)	.762
Hypercholesterolemia	118 (26)	100 (22)	.162
Thyroid disorder	107 (24)	70 (16)	.002
Depression	92 (20)	76 (17)	.171
Hypertension	91 (20)	95 (21)	.742
Rosacea	60 (13)	31 (7)	.001
Asthma	55 (12)	65 (14)	.327
Urticaria	43 (10)	36 (8)	.410
Panic syndrome	39 (9)	29 (6)	.207
Diabetes	28 (6)	32 (7)	.593
Rheumatoid arthritis	27 (6)	21 (5)	.373
Psoriasis	22 (5)	18 (4)	.518
Malignancies	14 (3)	4 (1)	.029
Vitiligo	9 (2)	4 (1)	.263
Lupus	9 (2)	4 (1)	.263

FFA, Frontal fibrosing alopecia.

Smoking cigarettes presented a negative relationship with FFA, suggesting a protective effect. In a review of 52 patients with FFA, there was a preponderance of nonsmokers in the group compared to the national data of the same country.[42] In another retrospective study, there was a higher prevalence of severe FFA among nonsmokers.[43]

Cigarettes contain thousands of chemical substances, and smoking presents a paradoxical behavior with intestinal inflammatory diseases, increasing the risk of Crohn's disease and having a protective effect against ulcerative colitis.[44] Actually, cigarette smoking impairs innate defenses against pathogens and modulates antigen presentation.[45] Dendritic cells exposed to cigarette smoking products decrease the production of interleukin (IL) 12 and IL-23, shifting the immune response to a Th2 pattern.[46-48] A recent report of overexpression of aryl hydrocarbon receptor in the epidermis from patients with FFA can support the link between cigarette smoking and FFA protection, because the activation of aryl hydrocarbon receptor suppresses cigarette smoke–induced oxidative stress, leading to the predominance of anti-inflammatory effects.[49,50]

Previous data have suggested a higher prevalence of premenopausal FFA status among black[6,51] or Hispanic/Latina women[52]; however, in this highly miscegenated sample, there was no association between earlier age at FFA onset and darker skin color.

FFA was associated with other autoimmune diseases.[4,16] Our results support the association with thyroid disorders. Actually, most thyroiditis is also due to $CD8^+$ lymphocyte infiltration and depends on an interferon-mediated response, which also occurs in FFA.[53]

The higher prevalence of rosacea in patients with FFA has already been described.[18] Additionally, it shares some epidemiologic and immunologic features with FFA. Adult women are more affected by rosacea than men are, smoking has a protective effect, and there is a Th1- and Th17-driven immunologic response.[54,55]

The potential limitations of this study lie in the recall bias and the slight baseline differences between the groups. To minimize selection bias, control individuals were selected from among patients from the same centers, but with noncicatricial alopecia. Moreover, the main results were adjusted for age, sex, and skin color.

Since its initial description, FFA has become the most frequent cicatricial alopecia, leading to a significant negative impact on patients' quality of life. This study reinforces the possibility of exogenous particles triggering FFA.

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