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Risk factors associated with frontal fibrosing alopecia: a multicentre case–control study

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Summary

Background. Frontal fibrosing alopecia (FFA) is a chronic cicatricial alopecia with an increasing incidence and unknown aetiology.

Aim. To identify possible environmental and hormonal factors related to FFA.

Methods. We conducted a multicentre case–control study paired by sex and age, and recruited 664 women (335 cases and 329 controls) and 106 men (20 cases and 86 controls). Study subjects completed an exhaustive questionnaire enquiring about pharmacological, environmental, hormonal, social, job exposure, lifestyle, drugs and diet factors to which they were exposed at least 5 years prior to the onset of the disease.

Results. For women, there was a statistical association between alopecia and history of pregnancy (OR = 1.6; 95% CI 1.06–2.41), use of facial sunscreen (OR = 1.6; 95% CI 1.06–2.41) and hormone replacement therapy (HRT) (OR = 1.76; 95% CI 1.11–2.8) or raloxifene (no controls exposed therefore OR was not calculated), exposure to alkylphenolic compounds (OR = 1.48; 95% CI 1.05–2.08), and presence of rosacea (OR = 1.91; 95% CI 1.07–3.39), lichen planus pigmentosus (LPP) (OR = 5.14; 95% CI 1.11–23.6) or hypothyroidism (OR = 1.73; 95% CI 1.11–2.69). For men, there was a statistical association between alopecia and use of facial sunscreens (OR = 11.6; 95% CI 1.7–80.9) or antiageing creams (OR = 1.84; 95% CI 1.04–3.23).

Conclusions. FFA seems to be associated with hormonal exposure (pregnancy, HRT and raloxifene), comorbidities (hypothyroidism, LPP and rosacea) and environmental factors (facial sunscreens, antiageing creams and occupational exposure). Further research is required to analyse the exact mechanism in which these environmental factors participate in the development of this alopecia.

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Introduction

Frontal fibrosing alopecia (FFA) is a primary lymphocytic chronic cicatricial alopecia with an unknown pathogenesis. There are no epidemiological records of this disease prior to its description by Kossard in 1994, but an apparent increase in its incidence has

been noted worldwide for the past decade.[1,2] Although the aetiology of FFA has not yet been elucidated, four factors have been postulated to participate in its aetiopathogenesis. First, genetic origin is suspected as family aggregation has been reported.[3] Second, sex hormones have been linked to the disease, as up to 95% of the incident cases of FFA are in postmenopausal women,[1] 5-alpha-reductase inhibitors seem to show efficacy in FFA treatment[1,2,4] and some publications have related FFA to gynaecological history.[1,2] Third, immune dysfunction may play a role in FFA development, as it has been noted to coexist with autoimmune diseases,[5] and has been associated with hypothyroidism[6] and lichen planus pigmentosus (LPP).[7] Finally, the relatively recent identification of FFA and its apparent increasing incidence[5] have been associated with environmental and dietary factors.[2,8] Recent case–control studies in both women[6] and men[9] have linked the disease with facial skin care products and sunscreens, although some controversy about this association remains.[10,11] Specifically, there are still some questions about the pathogenesis of FFA to be answered: (i) Are sunscreens truly associated with the disease? (ii) Do patients with FFA have an increased risk of autoimmune or fibrosing diseases? (iii) Is FFA related to occupation? and (iv) Is there any exogenous or hormonal factor involved in the disease? Based on these unanswered questions, we designed a case–control study with a double objective: to analyse topical sunscreens as risk factors for the disease, and to explore the potential association between FFA and other environmental, hormonal or autoimmune factors.

Methods

The study was approved by the Ramon y Cajal Hospital research ethics committee and conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent.

Patient selection

We conducted a multicentre case–control study paired by sex and age (± 5 years), which prospectively recruited 741 subjects from April to July 2017 in 13 centres throughout Spain. Inclusion criteria for cases were age > 18 years and a confirmed diagnosis of FFA by a dermatologist. Healthy controls (HCs) were randomly recruited from different groups including patients visiting the Dermatology Department for other reasons and both close contacts and unrelated people accompanying patients with FFA. All HCs were carefully examined by dermatologists to exclude the presence of scarring alopecia. Recruitment of HCs from healthcare professionals (e.g. nurses or doctors) was permitted but discouraged.

Study subjects completed an exhaustive questionnaire enquiring about pharmacological, environmental, hormonal, social, occupational exposure, lifestyle and dietary factors to which they were exposed at least 5 years prior to the onset of alopecia (for patients) or prior to study inclusion to the study (for HCs). In relation to the use of cosmetic products and intake of foods, it was decided to establish a weekly threshold for relevance. In the case of sunscreens and moisturizers, a daily application was considered relevant. Occupation was classified using the International Standard Classification of Occupations 1988 (ISCO-88)[12] and subsequently classified through an occupational exposure matrix that evaluated exposure to potential endocrine disruptors[13] (polycyclic aromatic hydrocarbons, polychlorinated organic compounds, pesticides, phthalates, organic solvents, bisphenol A, alkylphenolic compounds, brominated flame retardants, metals and 'miscellaneous').

Statistical analysis

Statistical data are presented as mean and range for continuous variables, and absolute and relative frequency for categorical variables. For the comparison between groups, we used Student *t*-test, Mann–Whitney *U*-test, Fisher exact test or χ^2 test, as appropriate. All *P*-values were two-tailed, and $P < 0.05$ was considered statistically significant. Use of topical sunscreens, moisturizers and antiageing creams was further assessed by multivariate logistic regression analysis using a backward stepwise selection approach. The Benjamini–Hochberg (B-H) procedure was used to control the false discovery rate (0.1) as multiple comparisons were performed. SPSS software (v23.0; IBM SPSS, Armonk, NY, USA) was used for all analyses.

Results

Participants

In total, 770 participants [354 cases (47.8%) and 387 HCs (52.2%)] were recruited. Of these, 664 were women (335 cases (50.4%) and 329 HCs (49.6%)] and 106 were men (20 cases (18.9%) and 86 HCs (81.1%)]. After pairing the subjects by age and sex, 578 women (289 cases

Table 1 Results for female participants.

Parameter	HC	Patient	*P*
Participants	289 (50%)	289 (50%)	
General history			
Age, mean (range)	58.4 (27–89)	60 (32–91)	0.10
Hobbies			
Indoor	54 (18.7%)	50 (17.3%)	0.66
Outdoor	235 (81.3%)	239 (82.7%)	
Rural upbringing	96 (33.2%)	85 (29.4%)	0.32
Sun exposure	154 (53.3%)	142 (49.1%)	0.31
Rural travel	78 (27%)	87 (30.1%)	0.4
Swimming pool use	170 (58.8%)	152 (52.6%)	0.13
Chemical exposure			
Organic solvents	90 (31.1%)	114 (39.4%)	< 0.05
Alkylphenolic compounds	90 (31.1%)	116 (40.1%)	0.03
PAHs	3 (1%)	2 (0.7%)	0.65
POCs	0	0	1.00
Pesticides	6 (2.1%)	4 (1.4%)	0.52
Phthalates	8 (2.8%)	8 (2.8%)	1.00
Bisphenol A	1 (0.3%)	1 (0.3%)	1.00
Brominated flame retardants	2 (0.7%)	2 (0.7%)	1.00
Metals	14 (4.8%)	12 (4.2%)	0.68
Miscellaneous	3 (1%)	5 (1.7%)	0.47
Cosmetics (minimum exposure once weekly)			
Facial sunscreen (daily)	101 (34.9%)	139 (48.1%)	< 0.01
Body sunscreen (daily)	1 (0.3%)	6 (2.1%)	0.06
Facial moisturizer (daily)	250 (86.5%)	259 (89.6%)	0.24
Body emollient (daily)	144 (49.8%)	143 (49.5%)	0.93
Antiageing/antiwrinkle creams	202 (69.8%)	225 (78.5%)	0.06
Hair products*	256 (88.5%)	259 (89.6%)	0.68
Foundation makeup	97 (33.5%)	89 (30.7%)	0.38
Food (minimum consumption once weekly)			
Soy products†	29 (10%)	42 (14.5%)	0.10
Herbs/spices‡	114 (39.4%)	96 (33.2%)	0.11
Grapes	39 (13.5%)	25 (8.7%)	0.06
Gynaecological history			
Hysterectomy	36 (12.5%)	36 (12.5%)	1.00
Any oophorectomy	22 (7.6%)	32 (11.1%)	0.15
Reproductive years	34.2 (17–48)	34.5 (15–52)	0.59
Pregnancy	219 (75.8%)	241 (83.4%)	0.03
Lactation	171 (59.4%)	200 (69.7%)	0.01
Oral contraceptives	143 (49.5%)	141 (48.8%)	0.86
HRT	34 (11.8%)	55 (19%)	0.02
Comorbidities			
Type I diabetes mellitus	3 (1%)	1 (0.3%)	0.30
Rheumatoid arthritis	11 (3.8%)	20 (6.9%)	0.09
Lupus erythematosus	0	1 (0.3%)	0.30
Vitiligo	1 (0.3%)	7 (2.4%)	0.06
Lichen planus pigmentosus	1 (0.3%)	9 (3.1%)	0.02
Rosacea	20 (6.9%)	36 (12.5%)	0.03
Dupuytren disease	0	1 (0.3%)	0.31
Visceral/peritoneal fibrosis	3 (1%)	1 (0.3%)	0.32
Arthrofibrosis	3 (1%)	2 (0.7%)	0.65
Hypothyroidism	38 (13.1%)	60 (20.8%)	0.02
Keloid	3 (1%)	7 (2.4%)	0.20
Breast cancer	13 (4.5%)	10 (3.5%)	0.52
Ovarian cancer	2 (0.7%)	0	0.15
Drugs			
Tamoxifen	5 (1.7%)	6 (2.1%)	0.76
Raloxifene	0	6 (2.1%)	0.03

HRT, hormonal replacement therapy; PAHs, polycyclic aromatic hydrocarbons; POCs, polychlorinated organic compounds. Data are *n* (%) unless otherwise stated. *Serum, shampoo, conditioner, dye or hairspray; †soybeans, miso, tofu, nattō/tempeh or soy oil; ‡ginger, oregano, rosemary, sage or thyme.

and 289 controls) and 77 men (19 cases and 58 controls) were analysed.

Women

Mean age was 60 and 58.4 years for cases and HCs, respectively. The evaluated variables are shown in Table 1.

History of pregnancy, lactation, hormone replacement therapy (HRT), raloxifene intake, daily use of facial sunscreen, exposure to organic solvents and alkylphenolic compounds, rosacea, LPP, and hypothyroidism were statistically associated with the disease in the bivariant analysis. Both vitiligo and antiageing creams showed a statistical trend towards significance. History of lactation did not remain significantly associated with FFA after adjusting by pregnancy. In the case of raloxifene, no HCs were exposed to the drug and therefore, risk was not calculated. Sparse data bias was suspected in the association between LPP and FFA, and was addressed via penalization.

Daily exposure to facial sunscreens was further analysed by multivariate regression analysis using as covariates age, sex, race, level of studies, geographical location, rural upbringing, sun exposure in summer, outdoor swimming pool use, outdoor hobbies and presence of photosensitizing diseases (rosacea, lupus or dermatomyositis). Adjusted OR for daily facial sunscreen use was 1.65 (CI 95% 1.15–2.40). No association between marital status, race, smoking status, alcohol consumption, specific foods (e.g. phyto-oestrogens), hobbies, contraceptive use, history of oophorectomy or hysterectomy, history of fibrosing diseases or total number of reproductive years was found.

Table 2 Results for male participants.

	HC	Patients	*P*
Participants	58 (75.3%)	19 (24.7%)	
General history			
Age, mean (range)	49.7 (20–78)	52.3 (21–78)	0.67
Hobbies			
Indoor	7 (12.1%)	0	0.11
Outdoor	51 (87.9%)	19 (100%)	
Rural upbringing	15 (25.9%)	4 (21.1%)	0.67
Computer use	37 (63.8%)	14 (73.7%)	0.42
Sun exposure	34 (58.6%)	12 (63.2%)	0.72
Rural travel	14 (24.1%)	6 (31.6%)	0.52
Swimming pool use	29 (50%)	9 (47.4%)	0.84
Chemical exposure			
Organic solvents	2 (3.4%)	3 (15.8%)	0.09
Alkylphenolic compounds	3 (5.2%)	2 (10.5%)	0.41
PAHs	5 (8.6%)	3 (15.8%)	0.37
POCs	0	0	
Pesticides	2 (3.4%)	2 (10.5%)	0.22
Phthalates	2 (3.4%)	2 (10.5%)	0.22
Bisphenol A	0	0	
Brominated flame retardants	0	0	1.00
Metals	7 (12.1%)	3 (15.8%)	0.67
Miscellaneous	0	0	
Cosmetics (minimum exposure once weekly)			
Facial sunscreen (daily)	4 (6.9%)	6 (31.6%)	< 0.01
Body sunscreen (daily)	1 (1.7%)	1 (5.3%)	0.4
Facial moisturizer (daily)	11 (18.9%)	10 (52.6%)	< 0.01
Body emollient (daily)	6 (10.3%)	4 (21.1%)	0.24
Antiageing/antiwrinkle creams	3 (5.1%)	7 (36.8%)	< 0.01
Hair products*	12 (20.6%)	3 (15.7%)	0.63
Aftershave	14 (24.1%)	7 (36.8%)	0.28
Food (minimum consumption once weekly)			
Soy products†	5 (8.6%)	2 (10.5%)	0.80
Herbs/spices‡	17 (29.3%)	6 (31.6%)	0.85
Grapes	3 (5.1%)	1 (5.3%)	0.98
Comorbidities			
Type I diabetes mellitus	1 (1.7%)	0	0.56
Rheumatoid arthritis	1 (1.7%)	1 (5.3%)	0.40
Lupus erythematosus	0	0	
Vitiligo	1 (1.7%)	0	0.56
Lichen planus pigmentosus	1 (1.7%)	0	0.56
Rosacea	0	2 (10.5%)	0.06
Dupuytren disease	0	0	
Visceral/peritoneal fibrosis	0	0	
Arthrofibrosis	0	0	
Myasthenia gravis	0	0	
Hypothyroidism	1 (1.7%)	0	0.56
Hyperthyroidism	3 (5.2%)	1 (5.3%)	0.98
Peyronie disease	0	1 (5.3%)	0.08
Prostate cancer	0	1 (5.3%)	0.08
Gynaecomastia	2 (3.4%)	0	0.41
Drugs			
Tamoxifen	1 (1.7%)	0	0.56
Raloxifene	1 (1.7%)	0	0.56

PAHs, polycyclic aromatic hydrocarbons; POCs, polychlorinated organic compounds. Data are *n* (%) unless otherwise stated. *Styling gel/hairspray; †soybeans, miso, tofu, nattō/tempeh or soy oil; ‡ginger, oregano, rosemary, sage or thyme.

Men

Table 2 shows the variables evaluated in men. Mean age for cases and controls was 52.3 and 49.7 years, respectively. Daily use of facial sunscreen, use of facial moisturizer and use of antiageing creams were statistically associated with FFA. Rosacea and exposure to organic solvents showed a statistical trend towards significance. As in women, daily use of facial sunscreen was analysed using a multivariate logistic model, resulting in an adjusted odds ratio (OR) of 11.6 (1.7–80.9). In the multivariate model, use of facial moisturizer failed to achieve statistical significance ($P = 0.06$) and adjusted OR for antiageing creams was 1.84 (95% CI 1.04–3.23). No other statistical significant association was found.

Further adjustment

All the variables for both men and women remained significantly associated with the disease after adjusting by B-H, except for exposure to organic solvents in women. Table 3 shows the final adjusted OR of every variable statistically associated with the disease in women and men.

Discussion

Although the aetiology of FFA remains unknown, its increasing incidence could be explained by environmental factors. Interestingly, in a multivariate analysis to control for possible confounding factors, our results supported the association between FFA and daily use of facial sunscreen in both women and men. Study subjects were also asked to enumerate their most used sunscreens, but the data provided were too heterogenous to analyse with statistical rigour. Nevertheless, most of the sunscreens used by the subjects were chemical sunscreens (data not shown). Future studies should focus on identifying those sunscreens and shared components.

The exact mechanism in which sunscreens might predispose to FFA has yet to be elucidated. There is an increasing number of experimental animal and *in vitro* studies that have linked commonly used sunscreens (e.g.

benzophenones) with endocrine modifications.[14] Owing to the scarcity of studies in humans, there is no conclusive evidence about the potential harmful effects of sunscreens. Nevertheless, topical sunscreens can enter systemic circulation and have been found in breast milk.[14] It is noteworthy that only facial, and not body, sunscreens were associated with alopecia in our study. This could be explained by a greater transcutaneous penetration of topical facial products due to pathological postmenopausal pilosebaceous involution. In addition, these molecules are widely used in other cosmetic products (e.g. foundations or antiageing creams). In fact, we observed a statistically significant greater use of antiageing creams in men with FFA, which is concordant with a previous study.[9] As these molecules have been shown to influence hormonal systems, they have been categorized as endocrine disruptors (EDs). EDs can be defined as exogenous molecules capable of altering endocrine functions and consequently of causing adverse health effects.[15] An ever-growing number of studies relate these molecules to significant endocrine modifications and, although controversial, to chronic diseases and human reproductive system disorders.[14,16]

EDs are also known environmental and occupational pollutants.[16] To assess the potential relationship between occupational exposure and FFA, we collected and analysed the occupations of our participants. For women, we found a statistically significant relationship between occupational exposure to alkylphenolic compounds. These xenobiotic molecules have oestrogen-disruptive capacity.[17] In addition to this, alkylphenolic compounds have been shown to interact with peroxisome proliferator-activated receptor (PPAR) γ[18] and to inhibit transformation of dehydroepiandrosterone (DHEA) to the sulphated form, DHEA-S.[19]

Table 3 Adjusted odds ratios for risk factors associated with frontal fibrosing alopecia.

	Women		Men	
Risk factor	OR	95% CI	OR	95% CI
Pregnancy	1.60	1.06–2.41	NA	NA
HRT	1.76	1.11–2.8	NA	NA
Raloxifene*	NA	–	NS	NS
Facial sunscreen	1.60	1.06–2.41	11.60	1.70–80.9
Antiageing cream	1.48	1.00–2.19	1.80	1.04–3.2
Alkylphenolic compounds	1.48	1.05–2.08	NS	NS
Rosacea	1.91	1.07–3.39	NS	NS
LPP	5.14	1.11–23.6	NS	NS
Hypothyroidism	1.73	1.11–2.69	NS	NS

LPP, lichen planus pigmentosus; HRT, hormone replacement therapy; NA, not applicable; NS, nonsignificant). *In the case of raloxifene, no healthy controls were exposed to the drug and therefore, risk was not calculated.

Interestingly, decreased PPARγ expression is involved in the development of lichen planopilaris in mice.[20] Moreover, it has been hypothesized that the pathological postmenopausal decrease in DHEA, which stimulates PPARγ, could be involved in the pathogenesis of FFA.[21] Finally, a recent study has shown androgen deficiency (e.g. low serum DHEA-S) in patients with FFA.[22]

Previous observational studies have reported a significant prevalence of autoimmune diseases in patients with FFA.[1,5,6] Our results support the association of FFA with hypothyroidism, rosacea and LPP in women. Therefore, based on these results, it seems reasonable to carry out tests to exclude these comorbidities in any female patient affected by FFA. Interestingly, this association was not found for men. The greater autoimmune tendency in women has been linked to sex hormones.[23,24] In situations in which there is an oestrogenic predominance, there is an immune shift to the lymphocyte T helper 2 response, increasing autoimmune risk.[23] In fact, it is known that certain autoimmune diseases such as lupus and primary biliary cirrhosis, which have been reported to coexist with FFA, may show clinical worsening with oestrogens but improvement with systemic androgens.[23] Prolactin has also been linked to autoimmune pathology.[24] In our study, we assessed several hormonal factors (pregnancy, HRT, raloxifene and alkylphenolic compounds) that directly or indirectly influence oestrogen and/or prolactin activity.[25] We know that premenopausal patients with FFA do not have altered serum hormonal levels,[26] and in fact, we did not find differences between cases and controls regarding total reproductive years as we previously thought.[1] We hypothesize that in genetically susceptible patients, an immune response may be triggered after exposure to exogenous (e.g. ED) or endogenous specific hormonal factors.

Other environmental factors were also evaluated. Although a recent study linked consumption of buckwheat and millet with FFA,[8] we did not find any association between phyto-oestrogens (i.e. soy) or natural PPARγ agonists (i.e. grapes) and FFA.

Lastly, we explored the possibility of an association with fibrosing comorbidities in patients with FFA, but found that there was no greater tendency to developing fibrotic conditions in patients than in HCs.

Although case–control studies are useful for diseases with an unknown or long latency, as in the case of FFA, they have inherent limitations. Firstly, selection and recall bias can influence the results of the study. To limit selection bias, controls were recruited from the same population groups as cases and were paired by age and sex. In addition, after collecting the occupations of the subjects, we verified that there was no unequal distribution of healthcare professionals recruited. We minimized the risk of recall bias

using the same questionnaire for cases and controls, blinding study subjects to the study hypothesis and allowing them enough time to answer the questions carefully. Lastly, case–control studies have statistical power only to suggest hypotheses and therefore, better-designed prospective studies are needed to confirm such hypotheses.

Conclusion

FFA seems to be associated with hormonal exposure (pregnancy, HRT and raloxifene), comorbidities (hypothyroidism, LPP and rosacea) and environmental factors such as daily use of facial sunscreens and occupational exposure to alkylphenolic compounds in women and with environmental factors only (daily use of facial sunscreens and antiageing creams) in men. Further research is required to analyse the exact mechanisms by which these factors participate in the development of FFA.

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What's already known about this topic?

- FFA has an unknown aetiology and an increasing incidence.
- Previous observational reports have noted an increased prevalence of autoimmune diseases associated with FFA.
- In addition, topical sunscreens have been linked to FFA.

What does this study add?

- In women, FFA is associated with autoimmune disorders (hypothyroidism, LPP and rosacea), facial sunscreens, occupational exposure to alkylphenolic compounds, and hormonal factors (pregnancy, HRT and raloxifene).
- In men, FFA is associated with facial sunscreens and antiageing creams.

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