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REVIEW ARTICLE

An update of the pathogenesis of frontal fibrosing alopecia: What does the current evidence tell us?

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ABSTRACT

Frontal fibrosing alopecia (FFA) is a primary patterned cicatricial alopecia with a complicated pathogenesis yet to be fully understood. FFA appears to be increasing in incidence worldwide, especially in the last decade. In order to consider current treatment options, we reviewed current evidence for its pathogenesis comprising immune-mediated, genetic, hormonal and environmental factors. Th1-mediated inflammation with collapse of hair follicle immune privilege and bulge epithelial stem cell destruction, peroxisome proliferator-activated receptor gamma (PPAR-γ) depletion and epithelial–mesenchymal transition are key events leading to permanent hair follicle destruction in FFA. Although the vast majority of cases are sporadic, familial reports of FFA implicate genetic or epigenetic mechanisms in its pathogenesis. The frequent onset of FFA in post-menopausal women, similar patterning and co-existence with female pattern hair loss, together with a reportedly good response to 5α-reductase inhibitors suggest a role for sex steroid hormones. The reported increasing incidence invites speculation for, yet unproven, environmental triggers such as sun exposure and topical allergens. More robust research into this unique entity is required to help understand the complexity of the pathogenesis of FFA in order to find satisfactory therapeutic targets for this often distressing condition.

Key words: 5α-reductase inhibitors, cicatricial alopecia, contact allergy, epithelial–mesenchymal transition, frontal fibrosing alopecia, immune privilege, pathogenesis, peroxisome proliferator-activated receptor gamma, sunscreen.

WHAT THIS RESEARCH ADDS

- Current evidence suggests that FFA is a unique entity and complex interactions between immune, genetic, hormonal and environmental contributions underlie its pathogenesis. Co-existence with female pattern hair loss and other hair conditions may explain why FFA is a challenging condition to treat and combination treatments are often required.

INTRODUCTION

First described by Kossard in 1994,[1] frontal fibrosing alopecia (FFA) is a primary cicatricial alopecia typically reported in post-menopausal women but is increasingly described in both pre-menopausal women and men. The incidence of FFA has increased in the last 10–15 years worldwide (Table 1) suggesting that this may either be a relatively new and evolving or a previously under-recognised and under-reported entity. The implications of this condition on health-related quality of life should not be underestimated.

Frontal fibrosing alopecia is now recognised as an extensive lichenoid and fibrosing disorder with multiple associated cutaneous sites (Table 2). The patterned presentation of FFA on the frontotemporal hairline is what distinguishes it from lichen planopilaris (LPP), which more

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Table 1 Case Series of frontal fibrosing alopecia (n = 42)

Years of publication	1994–2018
Countries (in alphabetical order)	Australia, Belgium, Brazil, Canada, Germany, Italy, Japan, Lithuania, Portugal, South Africa, Spain, UK, USA
Total number of patients reported	1524
Total number of Males	81
Total number of Females	1443
Average age at time of hair loss	54.9
Minimum age	18
Maximum age	88
Autoimmune disorders % average and range	
Thyroid disease	12% (0–33)
Other autoimmune disorder	24.8% (0–100)
Family history of FFA	17.7% (0–50)
History of Male or Female Pattern Hair Loss	38.6% (0–100)
Sites of involvement % average and range	
Eyebrow	74.6% (29–100)
Eyelash	10.3% (0–26)
Body	45.5% (5.6–100)
Occipital	13.2% (5–28.5)
Vertex	43.8% (14–100)
Beard	41% (8–77)

Table 2 Clinical features of frontal fibrosing alopecia

Common
Frontotemporal symmetric hair line recession with perifollicular erythema and scaling.
Pattern variants:
'Androgenetic alopecia-like' that is bitemporal hairline involvement with sparing of paramedian frontal hairline
'Cockade-like' or 'pseudo-fringe sign' that is sparing of a band of temporal hairline
'Diffuse' that is moth-eaten or zig-zag involvement of frontotemporal hairline
'Ophiasis-like' that is continuous band-like involvement from frontal to occipital scalp margins
Eyebrow loss that is lateral thinning, marked decrease or total loss
'Lonely hairs' (singular hairs on affected pale atrophic skin)
Facial Papules
Less common
Occipital scalp involvement
Loss of eyelashes, body hair, sideburns and beard areas (in men)
Glabellar red dots
Scalp hyperhidrosis
Depression of frontal veins
Hypo- or hyper-pigmented perifollicular macules

often affects the vertex of the scalp and tends to be multifocal. The histopathology of both conditions, however, is indistinguishable. In FFA, eyelash loss, facial papules and involvement of other body sites are associated with more severe disease.[2] The clinical history of FFA is typically one of slow progression over many years; however, rapid progression and self-limitation can also occur. It is generally asymptomatic, but may be associated with trichodynia and pruritus.

The complex pathogenesis of this disorder remains to be fully dissected and a number of causes and associations have been postulated. We reviewed the current English language literature and have considered the evidence under four main categories: immune-mediated, genetic, hormonal and environmental contributions. Understanding the pathogenesis of FFA is essential to help determine effective treatments for this condition, which to date, are still unsatisfactory and frustrating for patients and clinicians alike.

METHODS

The Ovid Medline electronic database was accessed for publications in English with relevant information pertaining to the pathogenesis of FFA up to 31st August 2018. In order to include the most up-to-date information in this review, relevant meeting proceedings (published and unpublished) at the 23rd World Congress of Dermatology (June 2015), and the 9th and 10th World Congress of Hair Research (November 2015 and November 2017, respectively) were also included in the analysis.

Pathogenesis

Immune-mediated

Pathogenic immune-mediated inflammatory mechanisms underlying FFA provide the most robust level of evidence for its pathogenesis thus far. Whilst similarities in underlying inflammatory patho-mechanisms with LPP and indistinguishable histopathology have conventionally led to the assumption that FFA is a variant of LPP, these alone do not fully explain the full phenotype of FFA.[3] Furthermore, the incidence of FFA has been reportedly increasing over the last two decades whereas this has remained relatively unchanged for LPP.[4]

There are three main immune-mediated and inflammatory mechanisms currently implicated in the development of FFA/LPP: (i) A Th1-biased inflammatory attack and resultant collapse of hair follicle (HF) immune privilege leading to the permanent destruction of epithelial HF stem cells (eHFSC).[5] Physiologically, HF immune privilege protects the eHFSC from potentially damaging immune responses through downregulation of MHC class I and II proteins.[6,7] The hair follicle has been shown to generate locally immunosuppressive agents such as transforming growth factor-beta 1 and 2 (TGF-β1 and β2), adrenocorticotropic hormone (ACTH) and alpha-melanocyte stimulating hormone (α-MSH) under physiological conditions.[5,6] A failure in these protective mechanisms and Th1-mediated inflammatory breach of hair follicle immune privilege in FFA/LPP lead to permanent destruction of the *bulge region* of the HF where eHFSC reside. eHFSC control follicular regeneration and entry into the next anagen phase.[8] Unlike alopecia areata and chemotherapy-induced alopecia, where the hair *bulb* is affected and hair loss is usually reversible, permanent destruction of bulge eHFSC in FFA/

LPP leads to progressive fibrosis of the entire HF unit and its inability to regenerate altogether[9]; (ii) Deficiency of peroxisome proliferator-activated receptor gamma (PPAR-γ) signalling leading to inhibition of lipid metabolism and peroxisome biogenesis with resultant pro-inflammatory lipid accumulation, infiltration of inflammatory cells and hair follicle destruction.[10] PPAR-γ expression in LPP scalps is significantly downregulated compared to normal skin,[11] and mice with PPAR-γ deletion from bulge eHFSC have been shown to develop progressive scarring alopecia.[11] In *ex vivo* studies, PPAR-γ agonists have been shown to be protective for eHFSC by downregulating HF inflammatory responses including TGF-β1 signalling and partially inhibiting epithelial–mesenchymal transition[12]; (iii) Epithelial–mesenchymal transition (EMT) of bulge eHFSC leading to loss of polarity of the hair follicle epithelium and a switch to a mesenchymal or fibrotic phenotype, similar to the process of wound healing.[13] EMT is speculated to dominate more in FFA than in LPP due to the more fibrotic clinical phenotype of the latter.[13] EMT is mediated by signals such as interferon-gamma, (IFN-γ), TGF-β1, and epidermal growth factor (EGF).[13]

Interestingly, cicatricial alopecias have a significantly higher rate of sebaceous gland atrophy compared to non-cicatricial alopecias (53% v 5%, respectively).[14] Atrophic or absent sebaceous glands are seen in FFA including in those with very early signs.[15] Loss of sebaceous glands has been shown to cause inner root sheath degradation, hair cycle disruption and progressive hair follicle fibrosis.[16]

It is still unknown what triggers or predisposes an individual to the hair follicle inflammatory attack in FFA and genetic factors are being sought. Meanwhile, trauma and psycho-emotional stress have been postulated. Of note, there have been four reports of the development of LPP/FFA following hair transplantation.[17] The authors postulated a Koebner phenomenon or the generation of a pro-inflammatory milieu that compromised the relative immune privilege of the transplanted hairs. Mouse studies have shown that perifollicular neurogenic inflammation can be induced by stressful stimuli leading to increased mast cell degranulation and production of inhibitory mediators for hair growth such as Substance P.[18] Upregulation of Substance P expression around the HF bulge region can mediate neurogenic inflammation and EMT leading to perifollicular fibrosis.[13] Substance P expression has been shown to differ between LPP/FFA lesional and non-lesional skin, as well as between lesional skin of LPP and FFA.[19]

Harries and colleagues[13] have predicted that IFN-γ and PPAR-γ targeted treatments would lead the future for FFA/LPP. The targeted treatment strategy of downregulating IFN-γ and upregulating PPAR-γ could be more effective than currently used non-selective immunosuppressive agents for both conditions. There are currently no clinically available IFN-γ agonists, but janus kinase (JAK) inhibitors have been repeatedly shown to inhibit IFN-γ and therefore may be useful for FFA/LPP.[20] JAK inhibitors show promise in alopecia areata where hair follicles are also similarly subject to immune privilege collapse via a Th1-mediated inflammatory response and IFN-γ unregulated signalling.[21] Pioglitazone, a PPAR-γ agonist, has been used as a treatment option for LPP/FFA over the last decade, but with mixed results.[22,23] Further clinical studies are needed to guide effective treatment dosing and safety of these medications for patients with FFA/LPP.

Finally, FFA has been reported to be associated with a number of autoimmune disorders[24,25] (Table 1). The most commonly reported association is with thyroid disease. This association, however, may be related to the predominance of peri-menopausal women with FFA in whom the likelihood of finding thyroid antibodies is three times more likely than in controls.[26] Other autoimmune disorders such as scalp discoid lupus erythematosus, vitiligo, lichen planus, lichen planus pigmentosus, Sjogren syndrome and other alopecias are also reported associations.

Genetic

Although a genetic link has not yet been established, a family history of FFA has been reported in 17.7% of affected individuals (Table 1). The mode of inheritance suggested is autosomal dominant with incomplete penetrance.[27] In a Spanish case series,[2] 8% of patients had a family history of FFA. In another study, Dlova and colleagues[28] reported seven families with FFA in which two affected individuals were men. More research into the genetics of FFA is greatly needed and we eagerly anticipate results from a genomewide association study of FFA from a combined cohort in the UK and Spain.[27]

In individuals without a family history and in whom FFA appears to occur in a sporadic fashion, epigenetic modification that regulates the expression or silencing of genes may play a role in determining FFA onset and clinical phenotypes. There is an increasing body of evidence to support the influence of environmental and lifestyle factors on epigenetic mechanisms, such as DNA methylation, histone modification and microRNA expression. A small case–control study ($n = 7$ for tissue samples and $n = 10$ for plasma samples) reported four circulating microRNAs to be highly predictive of FFA disease status.[29] Epigenetic studies of larger cohorts are needed to provide more robust evidence of epigenetic involvement in FFA.

Hormonal

The role of sex steroid hormones in FFA is speculative based on clinical observations of its disease behaviour.

Androgens are more commonly implicated in the pathogenesis of hair loss, whereas the role of oestrogens in hair growth and hair loss remains controversial. After menopause, circulating oestrogen levels plummet, whereas androgen hormone levels rise. The onset of FFA in the vast majority of reported cases is post-menopausal, but there are increasing reports of FFA in pre-menopausal women as well as in men, which would downplay the role of low oestrogens. Pre-menopausal onset of FFA has been reported in almost all case series, and in a case report as early as age 17 (Table 1). A recent retrospective review of

43 pre-menopausal women with FFA has shown no abnormality in their sex hormone profiles.[30] Age of onset of menopause, contraceptive history and the use of HRT have also not been found to be significantly associated with FFA.[31]

Individuals with FFA commonly have concurrent female pattern hair loss (FPHL) or male androgenetic alopecia (MAGA). A large Spanish retrospective review of FFA with 343 women and 12 men[2] reported that 40% of affected women had concurrent FPHL, and 67% of affected men had concurrent MAGA. It is well established that the pathogenesis of FPHL/MAGA is androgen-dependent and requires a genetic predisposition.[32] An American study of 168 patients with FFA/LPP that looked specifically at hormonal and endocrine dysfunction found that androgen deficiency was present in 32.1% of individuals with FFA.[33] Dehydroepiandrosterone (DHEA), important in the biosynthesis of androgen and oestrogen, has been shown to modulate PPAR-γ function and has strong anti-fibrotic effects.[34] A decrease in DHEA and androgens could therefore lead to a pro-fibrotic state in FFA. Although the main effect of 5α-reductase inhibitors is the inhibition of the conversion of testosterone to the more potent dihydrotestosterone, significantly reduced levels of DHEA sulphate (DHEAS) have been reported with finasteride therapy.[35] These findings pose the question of whether treatment with 5α-reductase inhibitors, finasteride and dutasteride, is truly beneficial to FFA as reported in various studies[36,37] or if the common concurrence of FPHL or MAGA confounds the reported treatment benefits. It is therefore still unclear if, how, and to what extent, 5α-reductase inhibitor treatment is beneficial in FFA.

Environmental

Current speculations for the role for environmental triggers in the pathogenesis of FFA stem from the assumption that this is a relatively new disorder with increasing incidence, especially over the last decade.

Retrospective data from a French and German registry for FFA presented in 2015 reported a delay in diagnosis of up to 24 years in at least one patient, thereby describing the onset of the disease prior to the original publication by Kossard in 1994.[38] Nevertheless, there is a paucity of epidemiological data, and it is not yet clear whether this apparently increasing incidence relates to improved diagnosis and heightened awareness, or whether this is a true increase in incidence caused by exposure to environmental triggers in genetically predisposed individuals. The quest, therefore, to find pathogenic environmental triggers for FFA is of great interest for many research groups.

Sun exposure has been speculated as an environmental trigger for FFA. The vast majority of FFA cases have been reported in fair-skinned Caucasians.[2,25,39,40] Frontal fibrosing alopecia in Asians, South Asians and black African individuals has also been reported. The classical site of involvement on the frontotemporal scalp is regularly photo-exposed compared to other scalp regions. A small Brazilian survey reported that 87% of their FFA cases complained of photosensitivity compared to 13% of controls.[41] A higher rate of sunscreen use was also reported in the cases, and the authors attributed this to the increased photosensitivity. Interestingly, a case series of FFA in mostly pre-menopausal black Africans ($n = 44$) reported that 55% of these cases were preceded by biopsy-proven lichen planus pigmentosus, a known photo-aggravated condition, by a mean of 14 months (range 6–36 months).[42] These observations suggest a role for sun exposure in the pathogenesis of FFA, although in what capacity remains unclear.

Four retrospective questionnaire-based studies conducted at tertiary dermatology hair clinics in the UK (105 affected women and 100 controls[31]; and 17 affected men and 73 controls[43]), Australia (224 affected women and 224 controls[44]) and Spain (354 affected women and 387 controls[45]) have reported higher recall of sunscreen use in cases compared to controls. The authors in the above studies speculated, however, that the sunscreens may play a pathogenic role in the development of FFA based on these findings. Limitations of these questionnaire studies include control group selection and the retrospective nature with possible recall bias (e.g. being asked to recall back 5 years or more). There was also a lack or absence of clarification about the timeline of exposure between sunscreen use and the onset of FFA, as the mean age of onset preceded the time period in question by several years. It is quite possible that as patients with FFA become more aware of their condition, they start to use more regular sunscreen and facial moisturisers to protect and camouflage the increasingly exposed pale atrophic skin of FFA. Authors of the above studies acknowledged that sunscreen use cannot explain a few aspects of FFA including (i) why many individuals in the general population who use sunscreen products do not develop FFA, (ii) many patients with FFA have not or do not use sunscreens regularly, (iii) occipital and more widespread involvement in FFA where sunscreens would not be applied. A true causal relationship between sunscreens and FFA cannot, therefore, be convincingly concluded at this point in time.

Aldoori and colleagues[31] patch tested some of their patients, presumably looking for possible cutaneous allergens that could be causing FFA. It is unclear how patients were chosen for patch testing but they found that 52.5% of these patients had a positive reaction, mostly to fragrance-related allergens but with no specific allergic reactions to sunscreens reported. A Brazilian study also reported a similar rate of positive patch test reactions to fragrances in patients with FFA but no significant reactions to sunscreen products or facial creams.[46] In fact, such a rate of positive patch tests within a population is not surprising. In a UK study, 56% of Europeans had positive patch tests[47] which is comparable to an Australian cohort at The Skin and Cancer Foundation of Victoria, where 66.5% had positive reactions (R Nixon, unpublished). Therefore, the significance of this rate of positive patch tests in a population with FFA is not at all clear and may not be particularly meaningful.

Sunscreen allergy is rare, at a rate of approximately 0.9% detected via patch testing.[48] A yet unpublished Australian study, found relevant allergic reactions to sunscreens in a comparable 1.1% of 7890 patients patch tested (R Nixon, unpublished), with no lichenoid, photo-lichenoid or follicular allergic reactions to sunscreens. If sunscreens are somehow involved in FFA pathogenesis, an allergic contact dermatitis mechanism would therefore seem very unlikely. Implicating sunscreens in the pathogenesis of FFA without robust evidence for a causal association may result in sunscreen avoidance with potentially serious repercussions, especially since many individuals with FFA already have significantly photo-damaged forehead and facial skin and are therefore at high risk of developing skin cancers.

A link between ultraviolet filters in hair care products and FFA has been speculated[49] but not proven. A small Indian case–control study reported higher use of hair dyes in their cases with FFA associated with acquired dermal macular hyperpigmentation seen on the frontal hairline.[50] Since photo-allergic reactions to para-phenylenediamine in hair dyes have been previously reported for acquired dermal macular hyperpigmentation unrelated to FFA, the authors speculated that photo-allergic contact dermatitis to hair dyes could also explain the preferential photo-exposed frontal hairline involvement in FFA. However, the authors did not mention whether they patch or photo-patch tested their FFA cases to confirm these speculations.

Finally, environmental toxins such as tobacco smoking, alcohol consumption and occupational exposures such as organic solvents have not been convincingly associated with FFA.[2,59] More research is necessary to identify environmental triggers.

CONCLUSION

Frontal fibrosing alopecia is a primary patterned cicatricial alopecia with a complicated pathogenesis yet to be fully understood, hence explaining current treatment challenges and the need for combination therapy. FFA appears to be increasing in incidence worldwide, especially in the last decade. Current evidence suggests that complex interactions between immune-mediated, genetic, hormonal and possibly environmental contributions underlie its pathogenesis. The involvement of immune-mediated inflammatory responses provides the strongest evidence for the role of genetic and epigenetic mechanisms in FFA as we await results from larger studies. The role of sex steroid hormones in FFA is currently speculative based on clinical observations of its disease behaviour, and no causal association with endogenous and exogenous sex steroid hormones has been shown. The association between environmental triggers such as sun exposure and topical allergens is also speculative and is yet to be proven. More robust research into this unique entity is required to provide us with a much better understanding of its pathogenesis and is the best chance we have for identifying effective treatments for this often distressing condition.

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