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# Frontal fibrosing alopecia: A new autoimmune entity?

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ABSTRACT

Frontal fibrosing alopecia (FFA) is a rare type of cicatricial alopecic band, with bilateral and symmetric progressive regression of the frontotemporal hairline. The specific mechanisms of development of FFA remain unknown. Due to several clues, including the presence of lymphocytic infiltrates and the association of FFA with other autoimmune disorders, we hypothesised that FFA may be a new autoimmune condition, and future research must be focused on this possible origin.

## Introduction

Frontal fibrosing alopecia (FFA) was first described by Kosard et al. in 1994 in six Australian postmenopausal women who showed a cicatricial type of alopecic band with bilateral and symmetric progressive regression of the frontotemporal hairline [1]. Some consider it a form of *liquen planopilaris* (LPP), which is characterised primarily by slowly progressive hair loss and scarring on the scalp near the forehead, the eyebrows, eyelashes and/or other parts of the body. FFA usually affects postmenopausal women over the age of 50 years and is an infrequent condition in men and younger women [2,3]. The incidence is greater in white-skinned women and it is very uncommon in women with dark skin. There is evidence suggesting that the condition is more common in women who use facial cosmetics, particularly sunscreens [4]. A total of 921 cases of FFA have been reported in literature; of these, only 29 patients were men (3.21%) [5]. Due to the high prevalence in postmenopausal women, some authors have proposed that hormonal factors are related with this disease aetiology. However, the exact cause of this condition remains unknown. In addition to the higher prevalence of autoimmune diseases in women than in men, the possible role of autoimmune factors may be implicated in this condition. In this manuscript, we reviewed the available data on the pathogenesis of FFA and proposed the hypothesis that this disease may be autoimmune in origin.

## Clinical manifestations of FFA

FFA typically affects Caucasian women in the postmenopausal age and is generally asymptomatic [6–8]. When present, the main characteristics of this kind of alopecia are regression in hair implantation, which is frontal in 100% of patients but can also affect the temporal and occipital areas and scarring signs in up to 96% of patients [7–12]. These scarring signs include atrophy, loss of follicular ostia, skin pallor and the 'lonely hair' sign [6,8,9].

Alopecia can also involve the eyebrows in up to 50%–95% of patients and is the initial form of presentation in up to 39% of cases [6–11]. The eyelashes may be affected in 3% of patients; other areas, such as the underarms, pubis and limbs, are rarely involved, with prevalence ranging from 0% to 77% [8,9,11].

Additional findings are perifollicular–reticular erythema, predominantly on the zygomatic arch and hyperkeratosis, which represents active disease [8–10]. Pruritus and facial papules may be seen in up to 72% of patients and may indicate greater severity; these are recognised by their skin-colour pattern, monomorphism and noninflammatory rough appearance [6–10]. Additionally, these abnormalities can be seen on the forehead, glabella, eyebrow skin, cheeks and chin.

The dermatoscopic findings of FFA are loss of vellus hairs, perifollicular erythema, peripilar white casts, translucent skin surrounding the hair shaft and loss of follicular openings. The other findings are

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perifollicular peeling, ramified capillaries, white patches that represent fibrosis, grey-blue perifollicular dots that correspond to melanocytes with phagocytic activity and white dots that mean pigment incontinence [13].

Some patients complain of pain, burning sensation and flushing. Furthermore, some studies have shown that 8 of 12 patients gradually developed macules that were rounded or had target-like pattern on areas of hair follicle loss [8,10]. The emotional impact of FFA should be highlighted; some patients even end up having their eyebrows permanently tattooed [11]. Traction hairstyles seem to aggravate the scenario [6]. The less prevalent but equally reported manifestations are depression of the frontal veins, pigmented facial macules and glabellar red dots [8,14].

## Is FFA an autoimmune disease?

Although the specific mechanisms for the development of FFA remain unknown, some descriptions in literature suggested and led us to propose an autoimmune hypothesis as its origin.

### *Genetic basis supporting the possible autoimmune origin of FFA*

Due to the low prevalence of the disease, a precise genetic cause has not been established for FFA. However, some clinical reports have shown a familial form of FFA, implicating probable genetic factors. One report showed that in three of four families, FFA occurred in siblings; the first of them who were diagnosed were women, and two of them were less than 30 years old; all the affected siblings had atypical demographic characteristics. Moreover, in general, affectation of FFA was reported to be up to 3% in men; in familial cases, the prevalence rises up to 12.5% [6]. Some examples of cases reports were those FFA diagnosed in 1) two sisters, who were 65 and 59 years old, respectively; 2) in a brother and a sister and 3) a female patient whose mother and first cousin were affected [6,15,16].

### *Immune evidence*

Several immunologic disturbances have been identified in patients with FFA. For instance, lymphocytic infiltrates predominate in the histopathological analysis (see below).

Other immunological abnormalities in FFA include modified expression of transforming growth factor beta-1 (TGF- β1), which enhances the expression of proteins in keratinocytes and fibroblasts and is involved in wound healing [17]. Even more interesting, levels of TGF-β1 are regulated by the alpha and gamma functions of the peroxisome proliferator-activated receptor (PPAR).

In a murine model, Josefowicz et al. found that mice with mutations in chromosome 11 presented with alterations of the PPAR function and that phenotype was associated with atrophy of both sebaceous glands and hair follicles, which then underwent a fibrotic process. In fact, PPARγ has two main functions in the hair follicle; one is to stimulate the sebaceous glands in order to preserve adequate development and activity of the hair follicles, and the other is to promote a functional epithelium in hair follicles by maintenance of stem cells. Furthermore, knockout mice that had the genes coding for the receptor appeared to have similar manifestations with those in LPP. In addition, areas affected by FFA had been shown to have a loss of PPARγ [18].

### *Hormonal factors in FFA pathogenesis*

The steroid hormones, which are a crucial substrates for androgen production, are mostly present in women in their pre-menopausal stages and seem to be implicated in the activation of the PPARs [19]. Evidence based on cultured fibroblasts obtained from patients with pulmonary fibrosis showed that under dehydroepiandostrenedione (DHEA) stimulation, there was low transition from myofibroblasts to fibroblasts and collagen production and high apoptotic rates [18]. This can explain the high prevalence of FFA in postmenopausal women. In addition, DHEA has a role in controlling PPAR function; gene transcription was shown to improve under adequate levels of this hormone [18]. It is worth saying that skin cells account for all the necessary structures to synthesise dihydrotestosterone (DHT) and testosterone from DHEA; the action of the steroid sulfatase found in sebocytes and monocytes in this process gives rise to an inflammatory status [19]. Another important enzyme is the 5 alpha-reductase (5alfaR), which converts testosterone in DHT, thereby, reducing the most potent circulating androgens. The isoform I is present in hair follicles of the skin, whereas the isoform II is found in the genitals, face, chest, scalp and other areas [20]. Although 5alfaR had been widely studied in the pathophysiology of androgenetic alopecia (AGA), some of its inhibitors are used to treat FFA [12].

### *Environmental factors*

Recent research has focused on finding the relationship between FFA and facial/skin products and demonstrated that people with FFA tended to use these cosmetics more regularly compared with healthy people. This prompted the hypothesis that these products contain particular components that are capable of triggering the cutaneous reactions [7]. Considering our autoimmune hypothesis, facial leave-on products and other chemical components may trigger the inflammatory process in genetically susceptible patients. Although this phenomenon has not been described in FFA, it may be extrapolated from several autoimmune diseases, in which environmental factors play a key role [21,22].

## Clinical evidence: the example of polyautoimmunity

A patient with an autoimmune disease is well known to have a higher risk of a second autoimmune condition; in fact, polyautoimmunity is present in up to 35% of patients [23]. In literature, some case series associated the presence of FFA with autoimmune diseases [24,25]. Discoid lupus erythematosus is the most common autoimmune disease associated with FFA, followed by Sjögren's syndrome and vitiligo [5,26–28]. Likewise, other diseases, such as hypothyroidism, had been related with FFA. Therefore, some authors recommended thyroid tests and neck ultrasound for patients who have been diagnosed with FFA [5]. However, the aetiology of the thyroid disorder was not reported in most of these cases; therefore, an autoimmune origin cannot be completely considered [29]. Furthermore, other comorbidities, such as dyslipidemia, hypertension and osteoporosis, have been associated with FFA [5].

### *Histolopathological findings supporting autoimmunity*

FFA is a primary scarring lymphocytic alopecia [30]. Primary scarring alopecias are a group of diseases in which the hair follicle is the main target of the inflammatory process; they are classified according to the cellularity of the infiltrate (i.e. lymphocytic, neutrophilic or mixed), and FFA belongs to the lymphocytic type [31,32]. In 1994, Kossard et al. described a series of FFA cases and identified the characteristic histopathological pattern to comprise a lichenoid lymphocytic perifollicular infiltrate at the isthmus level and hair follicle infundibulum, accompanied by perifollicular lamellar fibrosis at the same level as the infiltrate [1,33]. Some authors stated that FFA is a type of LLP, because of the undistinguished similarities in the histopathology findings. On the other hand, some authors proposed that these are two separate diseases because of some differences, such as the depth of the inflammatory infiltrate and involvement of the interfollicular epidermis, which is observed only in LPP [34,35]. However, description of specific findings that allow easier and adequate diagnosis is necessary. Nevertheless, the pathognomonic clinical manifestations are usually

enough to diagnose a patient, and histopathological confirmation is only required in approximately 50% of all suspected cases [5]. The presence of lymphocytic infiltrates suggested that some antigens in the hair follicle may become recognised by self-reactive lymphocytes, leading to lymphocyte migration, infiltration and possible proliferation.

## Hypothesis of FFA as an autoimmune disease

Autoimmune disorders comprise a group of conditions that can affect any part of the body. Structural and/or functional damage to tissues and organs is produced by inflammatory responses that are mediated by the adaptive immune system (i.e. cellular and/or humoral) against self-antigens as a consequence of a phenomenon called 'self-antigen loss of tolerance [36,37]. Autoimmune disorders are estimated to have a prevalence of approximately 5%–7% in the general population [38,39]. Similar to FFA, most of autoimmune diseases are considerably more frequent in women than in men, with a female-to-male ratio ranging from 10:1 to 1:1, depending on the particular pathology [36].

The 'loss of tolerance' phenomenon occurs as a result of the interaction among multiple factors, including genetic, hormonal and environmental [37]. When the adaptive immune system loses the self-antigen tolerance, the cell- and humoral-mediated immune adaptive effector mechanisms produce damage to the body tissues. Some of these mechanisms involve activation of the complement system via the classic pathway, formation and secondary deposition of immune complexes and cell-mediated cytotoxicity [40,41].

Almost all of these pathological conditions, such as systemic lupus erythematosus, Sjögren's syndrome, vitiligo and type 1 diabetes, share some characteristics that explain an autoimmune behaviour. In 1957, based on the Koch's postulates for the definition of an infectious disease, Witebsky and Rose mentioned the postulates for autoimmune disorder [42]. At that time, three postulates must be fulfilled for a disease to be considered of autoimmune aetiology: 1) the presence of an autoantibody or an auto cell-mediated response, 2) identification of the corresponding autoantigen; and 3) demonstration of an analogous autoimmune response that is induced in an experimental animal [42,43]. Although there was a deeper understanding of the pathophysiology of autoimmune diseases, some changes in the postulates were added through time [43]. Currently, the modified Witebsky's postulates state five criteria, including 1) the specific adaptive immune response is directed to the affected organ or tissue; 2) autoreactive T cells and/or autoantibodies are present in the affected organ or tissue; 3) autoreactive T cells and/or autoantibodies can transfer the disease to healthy individuals or animals; 4) immunisation with the autoantigen induces disease in animal models; and 5) elimination or suppression of the autoimmune response prevents disease progression or ameliorates the clinical manifestation [44].

Because of similar genetic and environmental factors among the autoimmune diseases, patients with one autoimmune disease can develop other concomitant autoimmune disorders (i.e. polyautoimmunity) [23,45]. A systematic literature review showed that about 34.4% of the cohort of 1083 patients shared the phenomenon of polyautoimmunity [23].

Different aetiologies have been proposed to explain the underlying pathophysiology of FFA. Recently, an experimental study demonstrated that melanocytes were primarily affected in individuals with FFA. This study showed significant decrease in the melanocyte count in the lesional biopsies of five patients with FFA [46]. On the other hand, patients with LPP did not show this decrease, suggesting different conditions of origin between LPP and FFA. There is more evidence on the possible relationship between FFA and hypopigmentation and the possible autoimmune response against melanocytes [47]. A retrospective study of FFA showed that two patients who had pre-existing vitiligo on the forehead further developed FFA on the same site; this suggested interrelated immunologic events and supported the hypothesis of polyautoimmunity [28]. Alopecia areata (AA) and FFA share some features, such as a perifollicular lymphocytic inflammatory infiltrate and association with other autoimmune disorders, such as autoimmune thyroiditis and vitiligo [47,48]. Some evidence showed that melanocytes from the basal layer of the hair follicle infundibulum are the most affected in AA, whereas melanocytes from the upper hair follicle might be affected in FFA; these can explain why AA is a non-scarring alopecia and FFA is a scarring alopecia [47,49].

FFA has also been associated with hypoandrogenism. As we previously mentioned, DHEA may have relevance in the pathophysiology of FFA, as explained by the presumable absence of an endocrinologic pathway mediated by PPARγ. However, hypoandrogenism in itself has been shown to be a risk factor for the development of autoimmune disorders [50]. Very few cases of men with FFA have been reported, and some of these cases were related with hypoandrogenism; this explains the preponderance of the disease in postmenopausal women, who were shown to have a 60% reduction in the DHEA serum levels [51]. Androgens are well known to provide a protective effect against the loss of self-antigen tolerance; this explains the sexual dimorphism of autoimmune disorders [52].

At this point, we present three possible factors to support the hypothesis that FFA is an autoimmune disorder. First is the presence of a possible autoantigen, in this case, the melanocytes. The second factor is the frequent association with polyautoimmunity, which supports an immunologic cause of this disease. The third factor is hypoandrogenism, which is in congruence with the epidemiological characteristics of FFA (i.e. more frequent in postmenopausal women, who have hypoandrogenism, and less frequent in men, who are not usually

**Table 1**
Key evidence fulfilling the Witebsky and Rose criteria for autoimmune disorders.

| Witebsky and Rose modified criteria | Evidence | Source |
|---|---|---|
| 1. The specific adaptive immune response is directed to the affected organ or tissue | The presumable adaptive immune response is directed against the hair follicle | Tosti et al. [30]<br>Tan et al. [31]<br>Olsen et al. [32] |
| 2. Autoreactive T cells and/or autoantibodies are present in the affected organ or tissue | A lymphocytic infiltrate is present in FFA, but self-reactive cells or autoantibodies have not been described | Kossard et al. [1,33]<br>Tane et al. [31] |
| 3. Autoreactive T cells and/or autoantibodies can transfer the disease to healthy individuals or animals | This has not been done | |
| 4. Immunization with the autoantigen induces the disease in animal models | The autoantigen might be some kind of protein contained in the melanocytes. Animal experiments have not been done | Katoulis et al. [47]<br>Trautman et al. [48]<br>Slominski et al. [49] |
| 5. Elimination or suppression of the autoimmune response prevents disease progression or ameliorates the clinical manifestations | Immunomodulatory drugs have been used in FFA and showed good results. Some of these include topical corticosteroids and topical tacrolimus | Fertig et al. [53] |

hypoandrogenic) and increases the risk of developing autoimmune disorders due to the loss of protection against loss of immune tolerance. A summary of the key evidence that fulfilled some of the Witebsky and Rose criteria is shown in Table 1.

Current research is focused on demonstrating the possible implication of autoimmunity in FFA, based on patients with FFA in the context of other autoimmune diseases, compared with patients with isolated FFA.

## Conflict of interest

All the authors declare not to have any conflict of interest.

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