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REVIEW ARTICLE

Frontal Fibrosing Alopecia: An Update on Pathogenesis, Diagnosis, and Treatment

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Abstract

Frontal fibrosing alopecia (FFA), first described by Kossard in the early 1990s, is a form of primary lymphocytic cicatricial alopecia characterized by selective involvement of the frontotemporal hairline and eyebrows. Since the original description, an increasing number of cases have been reported worldwide and the clinical aspects of the disease have been better characterized. However, the pathogenesis is still unknown and several hypotheses have been made about possible triggering factors, including hormones, neurogenic inflammation, smoking, UV filters, and ingredients in leave-on facial products. A genetic basis has also been hypothesized as the disease can occur in siblings and members of the same family. Besides its pathogenesis, research is also focused on treatment; FFA is a chronic condition and at present there is no validated or approved treatment for this disorder. Commonly prescribed topical treatments include corticosteroids, minoxidil, and calcineurin inhibitors. Systemic treatments include 5α-reductase inhibitors, hydroxychloroquine, and retinoids. Intralesional triamcinolone acetonide is also utilized, especially for the eyebrows. Other possible treatments include pioglitazone, naltrexone, tofacitinib, and lasers.

Key Points

Frontal fibrosing alopecia (FFA) is a primary scarring alopecia characterized by a lichenoid lymphohistiocytic infiltrate around the infundibulo-isthmic region of the hair follicle.

There are no pathological criteria, at present, to distinguish FFA from lichen planopilaris.

FFA is not limited to the scalp, but frequently affects the face and the limbs.

Due to the lack of randomized clinical trials and the lack of a control group in clinical studies, treatment of FFA is not evidence based.

The aim of treatment is to stop disease progression. This might be achieved with topical, intralesional, and oral treatments, often combined together.

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1 Introduction

Frontal fibrosing alopecia (FFA) was first described by Kossard in 1994 [1] as a form of primary lymphocytic cicatricial alopecia characterized by selective involvement of the frontotemporal hairline and eyebrows. He reported a group of six patients, all Caucasian postmenopausal females, presenting with a band of frontotemporal hairline recession associated with perifollicular erythema and a marked decrease, or complete loss, of the eyebrows.

Although clinical and dermoscopic presentations have been described over the years, the pathogenesis, histology, and effective treatments for FFA are still debated. Since 1994, hundreds of cases have been reported in the literature, with an increase in its incidence observed worldwide [2]. The reasons for such an increased incidence remain unknown; although awareness of this disease might be an explanation, it is difficult to believe that FFA went unrecognized for years even by hair experts.

FFA is a cicatricial alopecia and by the time the patient seeks medical advice part of the hair/eyebrows are permanently lost. This disease is, in fact, difficult to recognize in its debut because it is subtle and usually slowly progressive and patients often attribute their hair/eyebrow loss to aging, delaying medical consultation. Early recognition of the disorder would allow early treatment and eventually prevent disease progression. Although some authors

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believe that FFA settles spontaneously, our personal experience in treating a large number of patients with this condition suggests this is not correct.

2 Pathogenesis

Frontal fibrosing alopecia is much more common in postmenopausal females, but cases in young women and, more rarely, in men have been reported [3, 4]. FFA has been reported more frequently in Caucasian patients, but over the years several cases of African American [5, 6] and Asian [7] patients have also been described, probably previously misdiagnosed as traction alopecia, androgenetic alopecia, or alopecia areata.

FFA is a cicatricial alopecia and this means that the hair follicles are permanently replaced by a scar-like fibrous tissue. In FFA, as in lichen planopilaris (LPP), the infundibulo-isthmic (bulge) region of the hair follicle is attacked by an immune-mediated inflammatory infiltrate, characterized by a prevalence of $CD8^+$ T lymphocytes [8, 9]. Inflammation of the bulge area destroys the hair follicle stem cells, preventing hair regeneration. It has been hypothesized that loss of the follicular immune privilege, as in alopecia areata, and a peroxisome proliferator-activated receptor (PPAR)-γ deficiency might enable the inflammatory process to attack the stem cells in the bulge region and permanently destroy them [10]. PPAR-γ has a strong antifibrotic activity and its decline could correlate with the fibrogenic inflammatory process of FFA. The triggering factors that lead to immune privilege collapse/PPAR-γ deficiency, and consequent inflammation, are, however, still unknown.

The etio-pathogenesis of FFA remains to be elucidated, although numerous hypotheses have been proposed [11, 12]. A genetic basis has been hypothesized because FFA has been diagnosed in siblings and members of the same family [13]. Tziotzios et al. [14] proposed a possible autosomal dominant inheritance with incomplete penetrance. The fact that FFA develops later in life suggests that environmental factors may play a role in the development of this disease. It is also possible that FFA occurs in family members because they are exposed to the same triggers [15].

Although FFA is thought to be a variant of LPP, there is no reported association with HLA-DR1, as in classical lichen planus, and in its variant Graham Little-Piccardi-Lassueur syndrome [16]. Alleles that correlate with FFA have not yet been determined. A genome-wide association study involving researchers from the UK and Spain will possibly provide important information on the genetics of the disease (Sergio Vano Galvan, personal communication, 3rd Hair and Nails Symposium, Brasilia, Brazil, 1–3 November 2018).

Since FFA predominately affects postmenopausal women, can respond to 5α-reductase inhibitors (5ARI), and is commonly associated with androgenetic alopecia, hormones have been postulated as possible triggers. Androgens have been suggested to have a major role in the pathogenesis of FFA and a small study points out that DHEA (dehydroepiandrosterone) and DHEA-sulphate are essential for PPAR-γ activity, and their decline with menopause could explain the PPAR-γ deficiency described in FFA [17]. A recent study reported, despite a number of biases, early menopause as a promoter of FFA and the use of intrauterine devices as a protector [18]. However, a retrospective study instead associated FFA with androgen deficiency, compared with LPP which was more frequently associated with androgen excess [19]. Therefore, the role of hormones is uncertain and still debated. What is definitely sure is that FFA occurs in both in pre- and postmenopausal women, is relatively rare in males, frequently affects androgen-independent hairs such as the eyebrows, is not affected by hormone replacement therapy, and has had an increasing incidence since its first description in the early 1990s.

Increased scalp sweating [20] has been reported in some patients with FFA and, though the authors are unable to state if the two conditions are really associated, they suggest further investigation be conducted on neurogenic inflammation. In fact, antisweat therapy improved scalp itch and inflammation with disease stabilization. The authors hypothesized that the inflammatory process occurring in FFA may induce a sweating reflex or may modulate the sweat secretion. It is also possible that the increased sweating in the forehead and frontal hairline triggers and maintains the hair follicle inflammation.

A recent study [21] reported altered neuropeptide expression (substance P decreased and calcitonin gene-related peptide increased) in the scalp of patients affected by FFA. This might be responsible for a decrease in the density of epidermal nerve fibers, which could explain the FFA-associated clinical symptoms.

Finally, environmental factors such as leave-on cosmetics are under evaluation as potential triggers for FFA. Aldoori et al. [22] reported a doubled incidence of use of facial sunscreens in FFA patients compared with controls, with most of the FFA patients testing positive to fragrances on patch tests (especially to linalool hydroperoxide and balsam of Peru). An increased prevalence of sensitization to fragrances could reflect greater use of cosmetics in the FFA population, as suggested by another study [23]—even if this is not particularly meaningful. No association between FFA and other facial products, haircare products, and hairstyle procedures (especially perms or tractions) has been proven [22]. Aldoori et al. [22] speculate that the trigger for FFA might not be a specific ingredient of facial products, such as the UV filters, but rather their retention within the hair follicle

once applied to the skin, probably due to low sebum production in the affected patients. This prolonged retention could trigger an immunological response, as hypothesized by other authors [24]. UV filters could be a major culprit, since these were added to products in the late 1980s. Although Seegobin et al. [25] questioned the association between FFA and the use of facial leave-on products, a recent case–control study confirmed an increased use of sunscreen-containing facial products in FFA patients [26].

Brunet-Possenti et al. [27] detected titanium dioxide nanoparticles in the hair shaft of a patient with FFA. This result was confirmed by a recent study that detected titanium dioxide in the hair shafts of 16 patients with FFA and three control females, but not in a male control [28]. How titanium dioxide could then be involved in the pathogenesis of FFA remains unknown. We know that contact sensitization to titanium is not involved, as patch tests with titanium are negative in FFA patients [29]. We can speculate that titanium could penetrate the follicular ostia causing a lichenoid reaction, but it may also enter the cells due to the very small size of its particles. Definitive proof of its role in FFA requires a carefully designed and large prospective study [28].

Finally, Fonda-Pascual et al. [30] reported that tobacco exposure could reduce the severity of FFA, although they could not demonstrate that smoking is a protective factor.

3 Clinical Features

Although pathology does not allow FFA to be distinguished from LPP, the clinical features of FFA are very distinctive. FFA presents mainly as a band-like recession of the frontotemporal hairline. The alopecic skin is slightly atrophic, devoid of follicular ostia, smooth, and lighter than the chronically sun-exposed forehead skin (Fig. 1). In doubtful cases, when minimal photodamage is present, cocking of the eyebrows can help to localize the original hairline [31] (Fig. 2).

Recently, three clinical patterns of hair loss have been described, according to the different types of hairline recession described over the years [32]: linear, diffuse zig-zag, and pseudo-fringe. The linear pattern is the band of uniform frontal hairline recession in the absence of loss of hair density behind the hairline. The diffuse zig-zag pattern is the same as linear but with at least 50% decreased hair density. Pseudo-fringe hairline recession is a clinical presentation similar to traction alopecia (hence the term ‘pseudo’) where the fringe sign is the presence of some hair retained along the hairline (especially in the temporal area) ahead of the alopecic skin [33] (Fig. 3).

In the immediate hair-bearing skin, perifollicular erythema and/or follicular hyperkeratosis may be present (Fig. 4); although rare, these might result in itch. Vellus hair is totally absent and this absence, together with the lonely hair sign (one or few terminal hairs standing on the forehead remotely from the receding hairline), have been reported as typical of FFA [34, 35] (Fig. 5). Over the years, cases of isolated occipital or retro-auricular

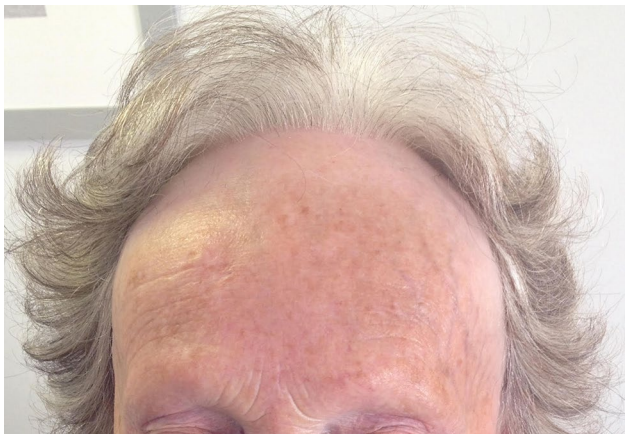

Fig. 1 Typical clinical presentation of frontal fibrosing alopecia: band-like recession of the frontotemporal hairline with loss of eyebrows. The alopecic skin is slightly atrophic, devoid of follicular ostia, smooth, and lighter than the chronically sun-exposed forehead skin

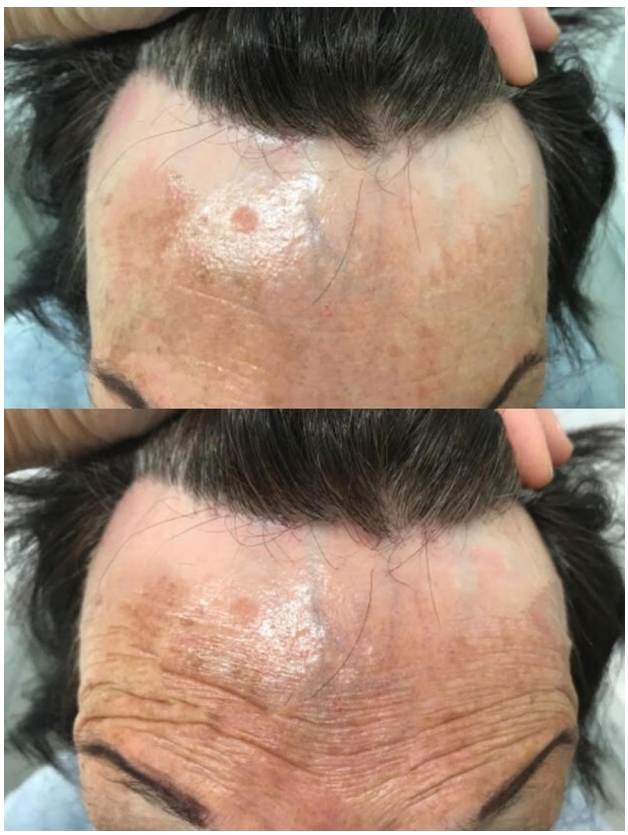

Fig. 2 Cocking the eyebrows is helpful to localize the original hairline

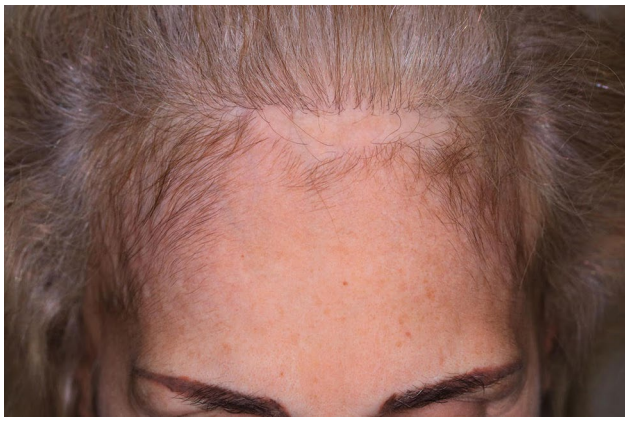

Fig. 3 Pseudo-fringe clinical pattern: some hair retained along the hairline ahead of the alopecic skin. Note that the eyebrows are maintained

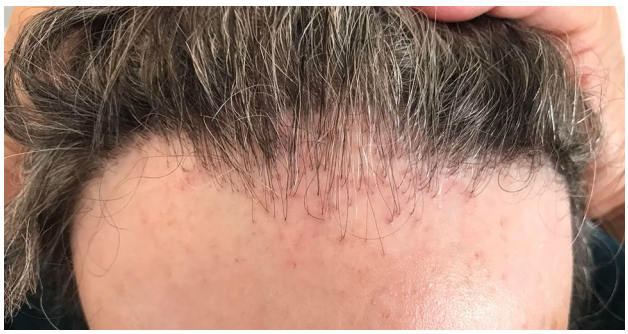

Fig. 4 Mild follicular hyperkeratosis and perifollicular erythema in the immediate hair-bearing skin

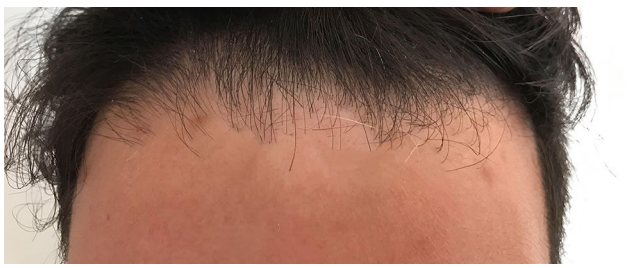

Fig. 5 The lonely hair: a terminal hair standing on the forehead remotely from the receding hairline

or sideburns FFA have been reported, establishing that this disease is not confined to the frontal scalp. Lateral or complete eyebrow loss, occasionally with perifollicular and interfollicular erythema, is another very common feature (Fig. 6). Typically, the 'pseudofringe' pattern of hair loss does not affect the eyebrows and this may lead to a delayed diagnosis of FFA. Eyebrow loss may precede

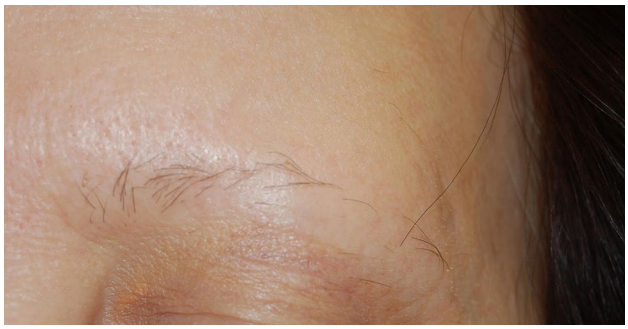

Fig. 6 Lateral or complete eyebrow loss is a very common feature of frontal fibrosing alopecia

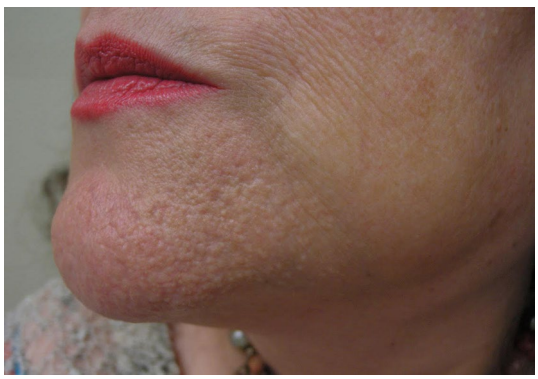

Fig. 7 Typical frontal fibrosing alopecia papules localized on the chin

or follow the hairline involvement, but it could also be the sole presentation of the disease, leading to a misdiagnosis of alopecia areata or senile eyebrow loss [36]. Volume loss has been reported for the eyelashes. Thinning of axillary, pubic, limb, and truncal hair, sometimes associated with follicular keratosis and/or erythema, can also occur before or after the scalp hair loss. These features are usually confused with age-related body hair loss and never reported by patients themselves [37–39]. Classic lichen planus in other scalp areas [40] or other body areas [41] as well as lichen planus pigmentosus [42, 43] may co-exist. Lichen planus pigmentosus is quite common in patients with dark phototype, where it is often misdiagnosed as melasma. Facial papules (forehead, cheeks, chin) (Fig. 7) [44], facial erythema [45], hypo-/hyperpigmented macules [45, 46], prominence, and, less often, depression [47] of the facial veins have also been described in FFA-affected patients. All these characteristics indicate that FFA is not limited to the scalp but also affects the skin. Facial papules indicate involvement of facial vellus hair, destroyed by the typical FFA inflammatory infiltrate [44]. In fact, pathology of established papules shows absence of the hair follicle with preserved sebaceous gland and no or minimal

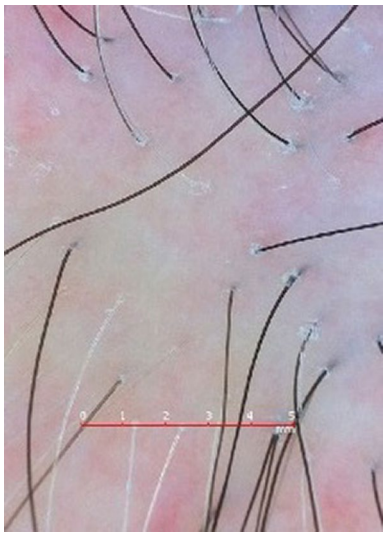

Fig. 8 Follicular hyperkeratosis (peripilar casts) and perifollicular erythema seen around terminal hairs with a handheld dermoscope

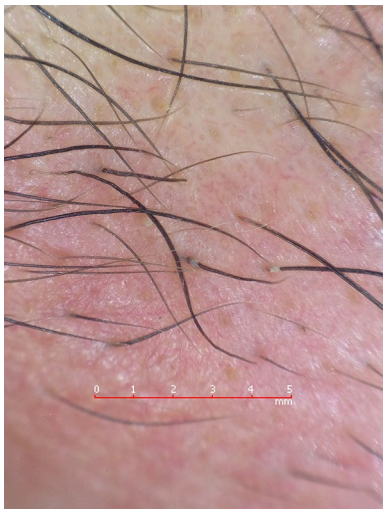

Fig. 9 Pili torti and broken hairs of the eyebrow area

inflammatory infiltrate [48]. Pirmez et al. [49] believe that reduction and fragmentation of elastic fibers are possibly responsible for the architecture of the papule remodeling the sebaceous gland, enlarging it, and leading to its popping out. In support of this hypothesis, facial papules improve with oral isotretinoin, which leads to atrophy of the sebaceous glands and improves the elastic fibers network [50]. Facial erythema, sometimes associated with follicular keratosis, may be diffuse or localized in the forehead and present as red dots [51]. When diffuse, erythema may cause a burning sensation and it is sometimes misdiagnosed as rosacea. This erythema is not related to corticosteroid use because most of the patients who presented with it had not started corticosteroid therapy. Recently, extra facial red dots/erythema have also been described as localized in the hip and upper chest of female patients with FFA [52, 53]. It has been speculated, once sun-induced erythema was excluded, that it could be an early manifestation of lichen planus pigmentosus. Pigmented macules are frequently localized along the scalp hairline and are a sign of pigmentary incontinence [45]. Depression of the frontal veins has been justified as a consequence of the overlying atrophic thin tissue [47]. All these clinical signs are related to FFA because at histopathology they show the typical lichenoid inflammation; however, interestingly, the infiltrate does not spare the interfollicular epidermis as it does in the frontal hairline of the scalp (see Sect. 4).

FFA is commonly associated with androgenetic alopecia, and frequently misdiagnosed as female pattern hair loss (FPHL) by non-hair expert dermatologists. FFA is commonly associated with FPHL, even though there are no studies showing that FPHL is more frequently observed in women with FFA than in age-matched unaffected women. Other associations with dermatological disorders include lupus, vitiligo, and Sjogren syndrome [54–58].

Clinical features of FFA are generally very suggestive, but trichoscopy (scalp dermoscopy) is a valid aid in doubtful cases/limited disease or when the eyebrows are the sole localization of the disease [59]. Even a handheld dermoscope reveals the cicatricial nature of this alopecia, showing reduced/absent follicular openings. Follicular hyperkeratosis (peripilar casts) and perifollicular erythema are seen around terminal hairs, but they may be very subtle (Fig. 8). These are signs of active inflammation, but not necessarily signs of disease progression [60, 61]. Absence of vellus hair is diagnostic and allows fast differentiation of FFA from androgenetic alopecia. Pili torti and broken hairs (Fig. 9) are commonly seen as well as black dots. Anzai et al. [36] reported red and gray dots in the eyebrows. All of these dermoscopic findings can help distinguish FFA from traction alopecia (white dots, broken and miniaturized hair), alopecia areata (presence of follicular ostia, yellow and black dots, exclamation mark hair, short regrowing hair), and androgenetic alopecia (presence of vellus hair, peripilar signs, and hair diameter diversity $>20\%$) [62]. FFA and traction alopecia are commonly associated and so the trichoscopic findings of the two disorders may coexist.

4 Histopathology

Frontal fibrosing alopecia shows different histopathologic presentations according to the stage at diagnosis. In early stages a lichenoid lymphohistiocytic infiltrate around the outer root sheaths in the infundibular and isthmus regions and a mild perifollicular lamellar fibrosis are present. Late

stages are instead characterized by more severe perifollicular fibrosis, with reduced follicular density until scar tissue replaces the pilosebaceous units. In 2006, Poblet et al. [63] wanted to determine if there are differences between FFA and LPP that could allow a diagnosis based solely on the histopathological picture. The authors noticed that sparing of the interfollicular epidermis from the inflammatory infiltrate (perivascular/periannexial infiltrate is absent) and eosinophilic necrosis of cells of the hair follicle outer root sheath (apoptosis) are distinctive characteristics of scalp FFA. Nevertheless, they were unable to demonstrate that FFA and LPP are two distinct histological varieties, but they suggested they be considered as variants of a bigger family of alopecia characterized by a lichenoid infiltrate. Wong and Goldberg [64] confirmed the previous findings and added that, in FFA, inflammation is localized predominantly in the lower part of the isthmus. The different depth of inflammation might explain the different and milder clinical scarring picture of FFA than that of LPP.

The 'follicular triad' has been reported as a histopathological clue to the diagnosis of early FFA [65]. The 'follicular triad' consists of the inflammatory infiltrate simultaneously involving vellus, intermediate, and terminal hair, at the same time and at different stages of cycling. Vellus and intermediate hair are more often targeted by the inflammatory infiltrate, probably because they are more numerous in the frontal hairline, but it is also possible that they are specifically the target because they express specific antigen inductors of the inflammatory infiltrate [66]. In order to find a difference between FFA and LPP, Donati et al [67] decided to evaluate whether direct immunofluorescence (DIF) could be useful, as it is in distinguishing LPP from lupus in doubtful cases [68], but in FFA the DIF patterns are too variable to be diagnostic. In general, however, DIF in FFA is negative. At present there are not enough differences between FFA and LPP that permit differentiating them only on the basis of histopathology and, for this reason, they are still considered variants of the same disease [69]. In general, the clinical presentation of FFA is different from LPP in that most of the time a biopsy to make the differential diagnosis is unnecessary, unless FFA presents in areas different from the frontal hairline.

5 Diagnosis

As stated earlier, the diagnosis of FFA can be made clinically with the aid of trichoscopy. Pathology is necessary only in the early stages or in uncommon/doubtful areas: the optimal biopsy site should be selected with the aid of trichoscopy [70].

Recently, a list of major and minor criteria has been proposed for the diagnosis of FFA [71]. Two major criteria or one major criterion and two minor criteria are required to diagnose FFA. Major criteria include cicatricial alopecia of the frontal/temporal/frontotemporal scalp (in the absence of follicular keratotic papules on the body) and diffuse bilateral eyebrow alopecia. Minor criteria include trichoscopic features, histopathologic features of cicatricial alopecia in the pattern of FFA and LPP, involvement of additional FFA sites (occipital area, facial hair, sideburns, body hair), and presence of non-inflammatory facial papules.

There are no specific laboratory tests that are useful for the diagnosis of FFA. A higher percentage of thyroid abnormalities have been detected in FFA patients than in the general population [3], but a link has never been demonstrated between the two diseases that justifies thyroid screening in all patients with FFA.

Optical coherence tomography has recently been utilized to investigate skin architecture and vascularization and proposed as a method for further follow-up [72]. Although the patient population studied was small, the results revealed increased epidermal thickness with irregular and reduced collagen distribution in the inflammatory hairline and decreased epidermal thickness in the alopecic band. The reduced amount of collagen means that cicatricial tissue in FFA is fibrotic rather than hypertrophic. Vascular flow in the alopecic band was decreased at superficial levels and increased at deeper levels compared with controls.

Once the diagnosis is made, the severity of FFA can be classified and in this way it can be monitored after treatment prescription. In 2016, Holmes et al. [73] proposed the first scoring system for FFA called the Frontal Fibrosing Alopecia Severity Index (FFASI), stating that a validated method for clinical practice and clinical trials was necessary. FFASI is compiled in two forms: A and B. FFASI-A utilizes clinical images of the hairline, divided into four sections. Alopecia severity is then graded 1–5 based on hairline recession. Other hair loss and additional features are also scored as no loss, partial loss, and total loss and present or absent, respectively. All scores may be combined to give a maximum score of 100. FFASI-B evaluates the same characteristics, but it includes scores to assess inflammation and density as well involvement of other body areas. Subsequently, other authors [74] criticized this scoring system as being too complex for clinical practice and because the clinical items included were assessed according to personal criteria without internal validity, and some were even doubtfully related to FFA. For this reason, a new scale has been proposed: the Frontal Fibrosing Alopecia Severity Score (FFASS). The FFASS evaluates hairline recession, eyebrows, perifollicular inflammation (severity and extent), and associated symptoms such as pruritus and pain. Although FFASS is

simple compared with FFASI, it also has limitations: it lacks trichoscopic evaluation and all evaluated patients were Caucasian females. These last points have been raised not only by the authors themselves, but also by other authors who have shown that patients of African and Asian descent may have LPP or traction alopecia associated with FFA. These associated disorders might confuse the clinical assessment and even overestimate FFA [75]. Recently, another scale, the Trichoscopic Visual Scale, has been proposed to correlate severity (thickness) of peripilar casts with severity of inflammation (lymphocytic infiltration) at pathology [76]. The scale shows three grades of severity, divided according to the number of lymphocytes (< 5; 5–10; > 5) per field at pathology. This scale needs to be evaluated prospectively to see if areas of most marked follicular hyperkeratosis correlate with progression of alopecia.

6 Treatment

Frontal fibrosing alopecia is a chronic condition and this means that patients need long-term treatments, even if at present there is no validated or approved treatment for this disease. The lack of randomized clinical trials does not allow definitive conclusions regarding the most effective of the available treatments. Moreover, the variable course of this disease and the possibility of spontaneous stabilization are at risk of overestimating the effects of the prescribed treatments. Commonly prescribed topical treatments are corticosteroids, minoxidil, and calcineurin inhibitors. Systemic treatments include 5ARI, hydroxychloroquine, and retinoids. Intralesional triamcinolone acetonide is also utilized, especially for the eyebrows. Newer possible treatments include pioglitazone, naltrexone, tofacitinib, lasers, and hair grafts (see Table 1). Treatment may differ according to disease localization, disease stage, and presence of inflammation and itch. Treatment may also change over time, depending on the patient's response. A recent study [77] demonstrated follicular inflammation around the infundibulum-isthmic region of the clinically unaffected scalp of FFA patients, indicating that treatment should involve the whole scalp.

Combination treatments are the most commonly utilized. In early inflammatory stages, especially when itch is present, topical corticosteroids are often prescribed [78], even though, in the authors' opinion, they are not a good option as they can worsen the skin atrophy that characterizes FFA and enhance interfollicular vascularization [79]. Topical tacrolimus is considered a valid alternative [80, 81]—it can be prescribed as a commercial cream or compounded in a solution with a better texture and which is easier for the patient to use. Topical minoxidil is utilized in FFA and is considered effective because of its in vitro antifibrotic properties that might prevent scarring [82], but also to control androgenetic alopecia, which is commonly associated with FFA. Intralesional triamcinolone acetonide can be used, for a more targeted treatment, both on the scalp hairline and on the eyebrows as monthly injections and at a concentration of 2.5 mg/mL. Higher dosages (up to 10 mg/mL) are considered to cause skin atrophy and are not recommended.

A recent review of studies on the efficacy of finasteride and dutasteride in patients affected by FFA [83] reported that only two studies have a moderate, although questionable, level of evidence [3, 33]. Nevertheless, the authors support the use of 5ARI because patients with FFA frequently experience a halt in disease progression. However, hair regrowth reported in some patients seems instead to be related to an improvement of concomitantly present androgenetic alopecia. The exact mechanism of action of 5ARI is still unknown and some authors disagree about their primary role in FFA treatment [84]. The use of 5ARI in women with childbearing potential is limited by their teratogenicity. Despite 5ARI having been reported to be protective from breast cancer by some authors [85], it is better to avoid their use in women with a personal or family history of breast cancer until more data are available. Decreased libido and mood disturbances have been described in men, but data in women are very scarce [86].

Table 1 Drugs dosages in frontal fibrosing alopecia-affected patients

Drug	Dosage
Clobetasol propionate 0.05% cream[a]	1/day overnight[b]
Tacrolimus 0.3–0.1% cream[a]	1/day overnight
Minoxidil 2% solution	2/day[b]
Minoxidil 5% foam	1/day (2/day in men)[b]
Triamcinolone acetonide 2.5 mg/mL	1/4–6 weeks (intralesional injections)
Finasteride 2.5–5 mg	1/day
Dutasteride 0.5 mg	1/day
Hydroxycloroquine 5 mg/kg	1–2/day (depending on total dose)
Isotretinoin 0.3 mg/kg	1/day overnight
Pioglitazone 15 mg	1/day overnight
Naltrexone 3 mg	1/day overnight
Tofacitinib 5 mg	2/day
Excimer laser; carbon dioxide laser	2–3/week (excimer laser); 1/2 weeks (carbon dioxide laser)
Hair grafts	

[a]The cream formulation is better tolerated by patients as ointment is too greasy (in the case of corticosteroid use, lotions and foam are alcohol based and too irritating). In cases of poor tolerance a compound with a body lotion could be made

[b]Do not apply just before bedtime to avoid contamination between the pillow and face (contamination increases the risks of adverse effects such as folliculitis and hypertrichosis)

Due to its anti-inflammatory properties, hydroxychloroquine is a valid option to treat FFA. Before starting hydroxychloroquine treatment, it is mandatory for patients to be checked by an ophthalmologist and undergo a complete blood examination (to exclude glucose-6-phosphate dehydrogenase (G6PD) deficiency and porphyria). Since retinopathy is the major adverse event during hydroxychloroquine treatment, according to the last ophthalmology guidelines the maximum daily dose should not exceed 5 mg/kg/day [87]. Other adverse events include nausea, abdominal pain, hepatitis, and skin rash. Smoking must be avoided or strictly reduced to better improve the efficacy of the drug. Precautions must be taken in women of childbearing potential as risks for the fetus include neurological disturbances and interference with hearing, balance, and vision.

A recent study by Rakowska et al. [88] reported an arrest of disease progression in the majority of patients using oral isotretinoin 20 mg/day and in those treated with acitretin 20 mg/day; results were superior to the control group treated with finasteride 5 mg/day. The mechanism of action of retinoids in cicatricial alopecia is not fully understood, but it could be anti-inflammatory and contribute to normalizing the antigen expression of the hair follicle keratinocytes. Notably, in contrast to all other drugs used to treat FFA, in this study there was no disease progression after discontinuation of treatment. As with the drugs already mentioned, precautions must be taken by women of childbearing potential and a complete blood examination is required before and during treatment.

Based on the findings that PPAR-γ is involved in scarring alopecia [12], the receptor agonist pioglitazone can be used to stimulate the activity of the receptor in patients with LPP and FFA. Pioglitazone is a hypoglycemic drug used to treat type 2 diabetes mellitus and its exact mechanism of action in cicatricial alopecia is still unclear. Due to the variable results reported in the literature and possible serious adverse effects, this drug is still under evaluation and more reports are necessary to establish its effectiveness. Positive reported results include stabilization of the disease with cessation of pruritus and fading of perifollicular erythema and hyperkeratosis. It has to be emphasized that pioglitazone has often used with other concomitant drugs such as finasteride, minoxidil, or corticosteroids, thus complicating correct evaluation of the results [89–91]. Due to lower-limb edema and weight gain, pioglitazone is often discontinued by patients. Other possible adverse effects include heart failure and increased risk of bladder, prostatic, and pancreatic cancer.

A novel treatment under evaluation in cicatricial alopecia is naltrexone at very low dosages. Naltrexone has been tested in patients with LPP and FFA [92] and, due to the positive results despite a very small sample size, could become an option to be tested in a larger cohort of FFA patients. Due to its anti-inflammatory properties, naltrexone seems able to reduce symptoms of pruritus, inflammation, and disease progression. Naltrexone is an opioid antagonist and patients should be aware not to take other opioids or alcohol during this treatment. Mood disorders, liver function, and personal medications have to be carefully revised before starting this treatment. As with the previous drugs, pregnancy should be avoided during treatment. Abdominal pain, nausea, headache, and anxiety are possible adverse effects.

Tofacitinib, a pan Janus kinase inhibitor, was recently tested in eight patients with LPP and two patients with FFA [93]. The rationale for its use lies in the inhibition of the interferon-associated inflammation. FFA-affected patients were treated with oral tofacitinib 5 mg twice a day for 6–9 months (in association with intralesional triamcinolone and hydroxychloroquine as adjunctive treatments), with improvement in the LPPA index. However, this study was retrospective and did not utilize trichoscopy to assess the degree of inflammation.

Finally, light treatments can also be an option in FFA, both alone and also as a complement to medical treatments. Excimer laser (UVB 308 nm) has been used to reduce inflammation expressed as erythema, pain, pruritus, and hyperkeratosis in patients with LPP and its variants, including FFA, with one session twice a week for an average of 11 sessions [94]. The rationale of excimer laser in FFA consists of its proven beneficial effect in other inflammatory skin conditions where a T cell apoptosis and cytokine expression alteration have been reported [95]. More recently, carbon dioxide laser (ablative fractional 10,600 nm) has also been tested in one patient affected by FFA. After 15 laser sessions, one every 2 weeks, the patient showed marked improvement in the texture of the alopecic skin [96]. The exact mechanism of action of this procedure is unknown but the treatment-induced wounds may contribute to hair follicle neogenesis. Among the adverse effects experienced during treatment, pain is the most frequent (cool devices or local anesthesia are necessary) and erythema, edema, and crusts generally occur after treatment.

Hair restoration surgery has been considered as a possible option. Other than a loose recommendation not to attempt surgery in patients suffering from cicatricial alopecia before 1–2 years of disease stabilization, no guidelines have been established so far [97, 98]. Unfortunately, the absence of signs and symptoms of inflammation for a prolonged period of time do not necessarily imply the disease is in remission and, if the disease reactivates, the transplanted follicles will be targeted by the same inflammatory reaction as the follicles they are replacing and may suffer the same fate. Even surgery itself, through koebnerization, can be responsible for disease reactivation. The literature also reports cases of FFA that have developed after hair transplant and facelift surgery [99], but it is not clear if the surgery induced the alopecia,

the alopecia was already present, but unrecognized, or it is just a coincidence. For these reasons, extreme caution has to be taken when considering hair surgery in FFA. Post-transplant medical treatment seems to be the difference between success and long-term maintenance: it is important to protect transplanted hair and prevent disease progression [100].

Trials are currently underway of oral apremilast (NCT03422640), topical gabapentin (NCT03346668), and platelet-rich plasma injections (NCT03335228) to establish their efficacy in FFA. They are still in the recruiting phase and no results are available.

7 Prognosis

Frontal fibrosing alopecia is generally a slow progressive disease, but rapid loss has been described [101]. Partial hair regrowth is possible during treatment, but it is very rare. Recently, Cranwell and Sinclair [102] reported a case of a perimenopausal woman showing hair regrowth within 6 months after stopping sunscreen use. The main objective of treatment should always be to stop disease progression and to reduce associated symptoms, especially itch. The evolution is unpredictable and each patient is different. A diffuse zig-zag pattern, presence of facial papules, and eyelash and body hair involvement are generally associated with a more severe prognosis. The pseudo fringe pattern has the best prognosis.

8 Conclusions

Frontal fibrosing alopecia is a disease that is still under research, with many groups currently focused on its pathogenesis and management. Recently, microRNA molecules (miRNAs) have been the object of investigation as potential markers of FFA activity. They are non-coding molecules involved in different cellular processes exerting target gene expression regulatory functions. They can be detected in plasma and serum and four different miRNAs have been identified [103] as specifically correlated with FFA activity. Larger studies are, however, necessary to validate these results.

Without a clear definition of the disease and a lack of a control group in clinical studies, treatment of FFA remains experience based instead of evidence based. Although FFA is not a diffuse form of alopecia with an acute onset (like alopecia areata), it has been associated with impaired quality of life due to the presence of symptoms such as pruritus and trichodynia, and due to frustration regarding the inability to control the course of the disease [104].

Compliance with Ethical Standards

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