Frontal fibrosing alopecia: clinical and prognostic classification


Dermatology Department, Ramón y Cajal Hospital, Madrid, Spain
*Correspondence: O.M. Moreno-Arrones. E-mail: o.m.m.arrones@gmail.com

Abstract

Background Frontal fibrosing alopecia (FFA) is a chronic scarring alopecia with an unpredictable evolution. There are no current classifications of this disease that may predict its prognosis.

Objective To analyse the differences in clinical presentation and evolution of FFA patients and to create a clinical and prognostic classification.

Methods We conducted a retrospective analytical study of FFA patients. Clinical characteristics of frontal hairline recession were used as the sorting variable between patterns of presentation. A cohort of 106 patients homogeneously treated with oral dutasteride and topical corticosteroid was followed 12 months.

Results In all, 242 female patients with a mean age of 61.4 years were included. Patients were classified into three clinical patterns [118 (48.8%) patients as pattern I (linear), 109 patients (45%) as pattern II (diffuse) and 15 patients (6.2%) as pattern III (double line)]. Stabilization was achieved in 37.3% of the 106 patients treated with oral dutasteride and topical corticosteroid. Pattern III patients had less hairline recession and eyebrow involvement at the diagnosis and after treatment.

Limitations Retrospective design.

Conclusions Frontal fibrosing alopecia patients can be classified into three different clinical patterns with different prognosis. Pattern III patients have the best prognosis, while pattern II patients have the worst prognosis.

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Introduction

Frontal fibrosing alopecia (FFA) is a primary scarring alopecia characterized by progressive recession of frontotemporal hairline, leaving a fibrosed band and atrophic skin. Eyebrow alopecia and facial hair involvement are commonly present.1

Frontal fibrosing alopecia has a chronic course. Stabilization of the disease may occur spontaneously or be induced by treatment.2,3 During the active phases of the disease, some patients refer pruritus or pain, and affected hair follicles may show signs of local inflammation, such as perifollicular erythema and hyperkeratosis.4,5 Other clinical signs such as facial papules, lonely hairs, glabellar red dots and depression of the frontal veins have been described without clearly stating its relationship with the activity of the disease.6–9

The evolution of FFA in each patient is unpredictable, and response to treatment is variable.4 Patients with similar clinical characteristics, such as extent of disease and time of evolution, can have completely different prognoses. The primary objective of this study was to analyse the differences in clinical presentation and evolution of FFA patients and to create a clinical and prognostic classification. The secondary objective was to predict response to treatment based on the proposed classification.

Methods

This single-centre observational and analytical retrospective study enrolled 242 female patients from 2010 to 2015 who received a diagnosis of FFA. The study was approved by the Ramón y Cajal Hospital Research Ethics Committee. Diagnosis
was made by clinical examination (recession of the frontotemporal hairline and eyebrow loss) and trichoscopy signs (perifollicular erythema, minor perifollicular hyperkeratosis and areas of loss of follicular openings) or based upon histopathology (scarring alopecia with a lymphocytic infiltrate) if atypical presentation or doubtful cases.

Information collected for the analysis included epidemiologic data (race, age and age of onset), medical and gynaecologic history, clinical presentation (frontal and temporal hairline recession pattern, eyebrow involvement, presence of perifollicular erythema and hyperkeratosis, glabellar red dots, facial papules, depression of frontal veins and lonely hairs) and treatment. In addition, we retrospectively analysed the evolution of a subgroup of 106 patients homogeneously treated with 0.5 mg oral dutasteride three times a week and topical clobetasol 17-propionate 0.05% foam twice weekly for 12 months.

To assess the growth of hairline recession and eyebrow involvement across time, clinical and trichoscopic findings taken at the 1-year follow-up were compared with the baseline images. Hairline recession was measured from the start of the primitive anterior hairline to the current anterior hairline not affected by alopecia. The posterior hairline was measured in patients affected by pattern III FFA. Eyebrow involvement was defined as complete if >75% eyebrow hair loss, partial loss between if 25% and 75% of eyebrow hair loss and no eyebrow loss if <25% of eyebrow hair loss.

Three clinical patterns of FFA were established based upon frontal hairline recession (Figs 1 and 2). Pattern I or 'linear pattern' was defined as a band of uniform frontal hairline recession in the absence of loss of hair density behind the hairline. Pattern II or 'diffuse pattern' was defined as a diffuse or zigzag band-like alopecia affecting the frontal hairline with significant loss of hair density behind the hairline (at least a 50% decrease in normal hair density) with a compatible trichoscopy of FFA (areas of loss of follicular openings, presence of lonely hairs, perifollicular erythema and minor perifollicular scaling). Pattern III or 'pseudo-fringe-sign pattern' was defined as a FFA presenting with a frontal or temporal unaffected primitive hairline forming the pseudo-'fringe sign.' Patients were classified according to the pattern of presentation; if a patient had a pseudo-fringe sign at the frontal and/or temporal hairline, she was classified as pattern type III. If the pseudo-fringe sign was not present, the frontal hairline was studied to classify the patient in either pattern type I or II.

Statistical data are presented as mean and range (continuous variables) and absolute and relative frequency (categorical variables). For the comparison between groups, we used the Student’s t-test, analysis of variance (ANOVA), Kruskal–Wallis test or

Figure 1  Clinical classification algorithm of FFA based on hairline recession.

Figure 2  Patterns of presentation of FFA. (a and b) Pattern I (‘linear pattern’); a band of uniform frontal hairline recession in the absence of loss of hair density behind the hairline can be observed. (c and d) Pattern II (‘diffuse pattern’); a diffuse or zigzag band-like alopecia affecting the frontal hairline with significant loss of hair density behind the hairline can be seen in these two patients. (e and f) Pattern III (‘pseudo-fringe-sign pattern’); pseudo-fringe sign is present at the frontal hairline of these patients.
The evolution of a subgroup of 106 patients (43.8%) who received the same treatment (oral dutasteride and topical steroid) was retrospectively analysed after a follow-up of 12 months. Mean age of patients was 62.2 years (range 33–87) and was not statistically different between groups, neither was the number of years of FFA evolution until diagnosis. Fifty-seven (53.7%) patients were classified as pattern I, 41 (38.6%) as II and eight (7.5%) as III. Significant statistical differences were found between patterns for each of the variables evaluated (Table 2). The majority of patients of pattern III (87.5%) had no progression 1 year after the diagnosis. In addition, their initial hairline recession (1.53 cm) was lower than the rest of groups. Only one patient experienced worsening of her alopecia by 0.20 and 0.15 cm, respectively, in frontal and temporal hairline. In
Table 2 Demographic and clinical characteristics of the cohort of 106 patients followed for 12 months. These patients were homogeneously treated with oral dutasteride and topical corticosteroids.

<table>
<thead>
<tr>
<th></th>
<th>Pattern I</th>
<th>Pattern II</th>
<th>Pattern III</th>
<th>Total</th>
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<tbody>
<tr>
<td>n</td>
<td>57 (53.7%)</td>
<td>41 (38.6%)</td>
<td>8 (7.5%)</td>
<td>106 (100%)</td>
</tr>
<tr>
<td>Years of alopecia evolution until diagnosis (\bar{P} = 0.703)</td>
<td>2.72 (range 0.5–10)</td>
<td>2.41 (range 0.4–8)</td>
<td>2.15 (range 1–4)</td>
<td>2.57 (range 0.5–10)</td>
</tr>
<tr>
<td>Age (years) (\bar{P} = 0.25)</td>
<td>60.5 (range 33–87)</td>
<td>64.4 (range 35–83)</td>
<td>62.2 (range 55–75)</td>
<td>62.2 (range 33–87)</td>
</tr>
<tr>
<td>Stabilization (\bar{P} = 0.002)</td>
<td>19 (33.3%)</td>
<td>5 (13.9%)</td>
<td>7 (87.5%)</td>
<td>28 (37.3%)</td>
</tr>
<tr>
<td>Initial hairline recession (cm) (\bar{P} = 0.008)</td>
<td>2.07 (range 1–10)</td>
<td>2.42 (range 1–7)</td>
<td>1.53 (range 0.85–2.5)</td>
<td>2.19 (range 1–10)</td>
</tr>
<tr>
<td>Final hairline recession (cm) (\bar{P} = 0.000)</td>
<td>2.60 (range 1–11)</td>
<td>3.40 (range 1–8)</td>
<td>1.73 (range 0.85–3)</td>
<td>2.89 (range 1–11)</td>
</tr>
<tr>
<td>Frontal increment (cm) (\bar{P} = 0.003)</td>
<td>0.63 (range 0–5)</td>
<td>0.96 (range 0–4)</td>
<td>0.20 (range 0–1)</td>
<td>0.74 (range 0–5)</td>
</tr>
<tr>
<td>Temporal increment (cm) (\bar{P} = 0.002)</td>
<td>0.24 (range 0–2)</td>
<td>0.48 (range 1–2)</td>
<td>0.15 (range 0–0.5)</td>
<td>0.33 (range 0–2)</td>
</tr>
<tr>
<td>Initial eyebrow involvement (\bar{P} = 0.000)</td>
<td>No eyebrow loss 4 (7%), partial eyebrow loss 25 (43.9%), complete eyebrow loss 28 (49.1%)</td>
<td>No eyebrow loss 6 (14.6%), partial eyebrow loss 18 (43.9%), complete eyebrow loss 17 (41.5%)</td>
<td>No eyebrow loss 8 (100%)</td>
<td>No eyebrow loss 18 (16.9%), partial eyebrow loss 45 (42.4%), complete eyebrow loss 43 (40.5%)</td>
</tr>
<tr>
<td>Final eyebrow involvement (\bar{P} = 0.000)</td>
<td>No eyebrow loss 3 (5.3%), partial eyebrow loss 19 (33.3%), complete eyebrow loss 35 (61.4%)</td>
<td>No eyebrow loss 5 (12.2%), partial eyebrow loss 10 (24.4%), complete eyebrow loss 28 (63.4%)</td>
<td>No eyebrow loss 6 (75%), partial eyebrow loss 2 (25%)</td>
<td>No eyebrow loss 14 (13.2%), partial eyebrow loss 31 (29.2%), complete eyebrow loss 61 (57.5%)</td>
</tr>
<tr>
<td>Final frontal perifollicular erythema and hyperkeratosis (\bar{P} = 0.552)</td>
<td>11 (19.3%)</td>
<td>8 (19.5%)</td>
<td>0</td>
<td>19 (18.4%)</td>
</tr>
<tr>
<td>Final temporal perifollicular erythema and hyperkeratosis (\bar{P} = 0.76)</td>
<td>5 (8.8%)</td>
<td>4 (9.8%)</td>
<td>0</td>
<td>9 (8.8%)</td>
</tr>
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cm, centimetres.

In contrast, pattern II patients had the worst initial hairline recession (2.42 cm), final hairline recession (3.40 cm), and frontal (0.96 cm) and temporal (0.18 cm) increment of recession. Five patients (13.88%) with pattern II remained stable after 1 year. Pattern I patients had values for the aforementioned variables in between patterns II and III. Regarding eyebrow involvement, pattern I and II patients had similar involvement after 1 year (>60% of patients with complete eyebrow loss). Pattern III patients had no initial eyebrow affectation, and only two patients (25%) experienced partial eyebrow loss after 1 year. After 1 year of treatment, perifollicular erythema and hyperkeratosis had decreased \(\bar{P} = 0.01\) in all the patients but showed no statistical difference between patterns.

Frontal fibrosing alopecia clinical signs were studied. Presence of facial papules at the diagnosis was associated with both initial eyebrow involvement \(\bar{P} = 0.012\) and final eyebrow involvement \(\bar{P} = 0.029\). Depression of frontal veins was associated with a worse initial hairline recession \(\bar{P} = 0.022\), and initial and final eyebrow involvement. Presence of lonely hairs at the diagnosis was associated with a worse initial and final hairline recession. Glabellar red dots were not associated with a worse hairline recession or eyebrow involvement.

The association between hairline recession and various clinical variables was assessed by multivariate linear regression analysis. Age, initial hairline recession and pattern type remained statistically significant in the multivariate analysis. A model to predict final hairline recession was created (Table 3).

**Discussion**

Despite the growing number of publications about FFA, little has been reported about the different clinical presentation and evolution between FFA patients. To date, although some forms of atypical presentation of this scarring alopecia have been described, no effort has been made to group these patients in patterns of presentation. In the present study, we propose a clinical and prognostic classification based on three patterns of presentation. We decided to use the frontal hairline recession as the sorting variable for several reasons: it is one of the defining features of FFA, it is easy to evaluate at the diagnosis and follow-ups, and it does not require additional complementary tests.
Table 3  (a) Multivariate analysis (b) Standardized beta-coefficients from multivariate linear recession model of determinants of final hairline recession.

<table>
<thead>
<tr>
<th>(a) Model</th>
<th>Adjusted $R^2$</th>
<th>Standard error</th>
<th>$P$</th>
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<tr>
<td>$a = (Equation \ y = \beta_0 + \beta_1 \times \text{age} + \beta_2 \times \text{initial recession} - \beta_3 \times \text{Pattern I} - \beta_4 \times \text{Pattern III})$</td>
<td>0.814</td>
<td>0.71</td>
<td>0.000</td>
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</table>

<table>
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<tr>
<th>(b) Model a</th>
<th>Unstandardized $\beta$ (95% CI)</th>
<th>$P$</th>
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<tr>
<td>$\beta_0$</td>
<td>$-0.319 (-1.155, 0.516)$</td>
<td>0.45</td>
</tr>
<tr>
<td>Age, per year</td>
<td>$0.019 (0.005, 0.033)$</td>
<td>0.007</td>
</tr>
<tr>
<td>Initial hairline recession, per cm</td>
<td>$1.028 (0.908, 1.148)$</td>
<td>0.000</td>
</tr>
<tr>
<td>Pattern I</td>
<td>$-0.358 (-0.665, -0.062)$</td>
<td>0.018</td>
</tr>
<tr>
<td>Pattern III</td>
<td>$-0.714 (-1.395, -0.034)$</td>
<td>0.040</td>
</tr>
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cm, centimetre.

This classification is based on physical examination exclusively; we did not find any histopathological differences between the patterns. The proposed classification may enable the clinician to perform an initial prediction of the evolution of the alopecia and act accordingly. Furthermore, it establishes common clinical phenotypes of FFA that may be useful for understanding potentially different pathogenic pathways.14

Pattern type III or ‘pseudo-fringe-sign pattern’ is the less frequent but interestingly has the best prognosis. These patients present with less hairline recession, eyebrow involvement, perifollicular erythema and hyperkeratosis, facial papules, glabellar red dots and depression of frontal veins than the other two patterns at the diagnosis. In addition, the majority of them remained stable with treatment. Eyebrow involvement was significantly rarer and slower than the other two patterns. This pattern shows the pseudo-‘fringe sign’, previously described by Pirmez et al.10 as a retention of the hairs along the frontotemporal hairline in patients with FFA. In this case series of 16 patients, two patients (12.5%) presented facial papules, one patient (6.2%) presented glabellar red dots and 11 patients (68.7%) had eyebrow involvement. Unfortunately, the authors did not specify the severity of eyebrow involvement or time of evolution of the alopecia. In our series, no patient had a history of traction hairstyle.

This pattern has a lower tendency to involve facial hair and hairline. It has been hypothesized that hair follicles may present a different antigenic profile in each phase of the hair growth cycle and in certain skin areas are less likely to be subject of autoimmune responses due to delicate local immunoregulation.18,19 Nevertheless, the exact mechanism of sparing of this area of the hairline needs further research to be elucidated.

Pattern type II or ‘diffuse pattern’ is the second most common presentation and has the worst prognosis. At the moment of diagnosis, these patients have significant higher hairline recession and perifollicular erythema and hyperkeratosis. In addition, the majority of the patients (86.1%) progressed in spite of the treatment. This recession of the frontal (0.96 cm) and temporal (0.48 cm) hairline is also significantly higher. This diffuse alopecia might be easily misdiagnosed as androgenetic alopecia or fibrosing alopecia in a pattern distribution when occurs on the frontal hairline.20–23 Nevertheless, our cases with pattern II FFA showed the same diffuse hair loss in non-androgenic dependent areas, such as sideburns and low temporal regions. In addition, these patients showed specific trichoscopic signs of FFA such as perifollicular scaling and small areas with loss of follicular units23 behind the hairline.

Pattern type I or ‘linear pattern’ is the most common (48.8%). It has an intermediate prognosis. A third of the treated patients did not progress after 1 year of follow-up. The rest of the patients who did not receive oral antiandrogens progressed with a mean frontal and temporal increment of 0.63 and 0.24 cm, respectively. Although pattern I has a lower frequency of perifollicular erythema and hyperkeratosis than pattern II, we found no differences between the frequency of other typical FFA clinical signs. Regarding eyebrow involvement, both patterns I and II have a similar affection at the diagnosis and at the follow-up: more than 60% of the patients had complete eyebrow loss after 1 year of treatment.

The usefulness of analysing data with a multivariate model was mainly for an explanatory purpose. It demonstrated how variables intuitively associated with a worse outcome of FFA as...
age or severity of hairline recession at the time of diagnosis is statistically associated with a worse outcome of the alopecia. It has also helped us to confirm that patients could be classified into three different groups with significant differences in their prognosis. In addition, it also showed that associations between FFA clinical signs and hairline recession disappear in the multivariate model. Probably, these clinical signs are good markers of the presence of lymphocytic cicatricial alopecia but poor predictors of severity. In fact, in our experience, some cases of FFA show persistent signs of inflammation such as perifollicular erytheme or hyperkeratosis without progress for many years, and this observation has also been noted by other authors.3,5

Finally, although it was not the primary aim of this study, we indirectly evaluated the effectiveness of dutasteride and topical corticosteroid treatment. Unfortunately, due to the clinical inconsistency of the disease and the heterogeneous treatments and measures published in the literature, it is difficult to compare results between studies. We analysed 106 FFA patients who received the same treatment. Approximately one-third of these patients (37.33%) remained stable. The rest of the patients had a monthly frontal and temporal hairline recession of 0.6 and 0.3 mm, respectively. A previous report of 13 patients treated with daily 0.5 mg oral dutasteride for 1 year stated that six patients (46.15%) did not progress, two patients (15.3%) improved and five patients (38.4%) experienced a 0.2 mm monthly hairline recession.24 In another study, 18 patients were treated with 0.5 mg oral dutasteride either weekly or three times a week, achieving stabilization in 56% of patients.4 In the same study, 94% of untreated patients (74 of 79) experienced a hairline progression of 0.9 mm monthly (10.5 mm annually). On the other hand, a published series of 18 patients treated with non-systemic corticosteroids, topical tacrolimus or hydroxychloroquine but without oral antiandrogens showed an average monthly progression of 0.9 mm, significantly higher compared to the patients treated with oral dutasteride. All these data support the effectiveness of dutasteride as oral treatment of FFA. Optimal dosage remains a controversial topic. Nevertheless, all the evidence of its usefulness is based upon observational studies.

Limitations of this study must be noted. Firstly, it is of retrospective design. Secondly, almost all the patients were Caucasian. Thirdly, the follow-up interval for this analysis might be short (12 months) considering the natural history of FFA. Nevertheless, it was enough to identify significant differences between the clinical patterns. By all means, the objective of this study was not to evaluate the exact progression of FFA, but to describe the different clinical patterns with different evolution that can be seen in this disease. Our results may be useful in daily clinical practice and could help to design future studies to assess the efficacy of therapies in each FFA pattern.

In conclusion, FFA patients can be classified into three different clinical patterns at the diagnosis. These three patterns have different prognoses. Patients classified as pattern III tend to progress slower and have lower involvement of eyebrows, while patients classified as pattern II or ‘diffuse pattern’ have the worst prognosis.

References
